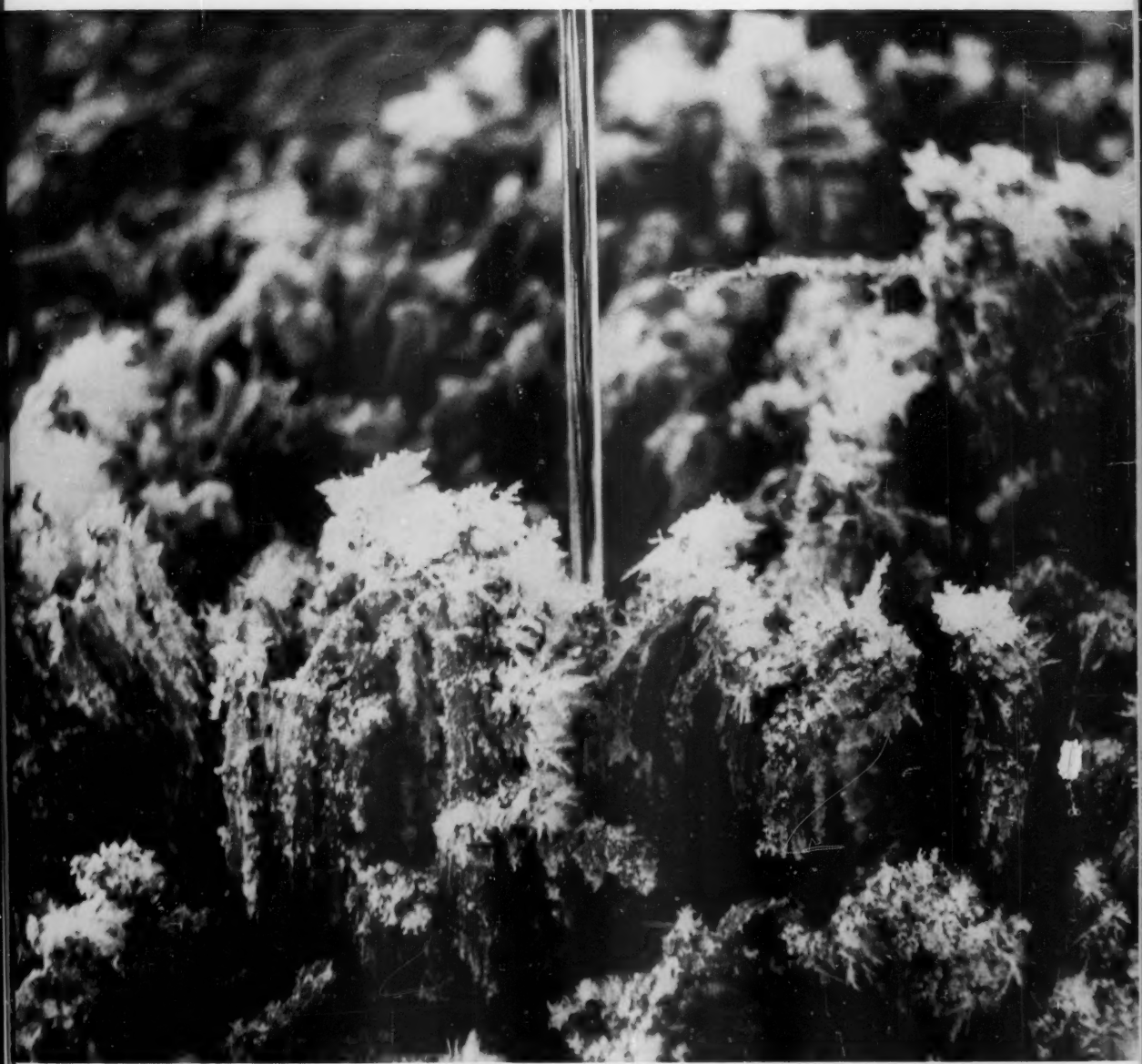
# SCIENCE

7 July 1961

Vol. 134, No. 3471

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE



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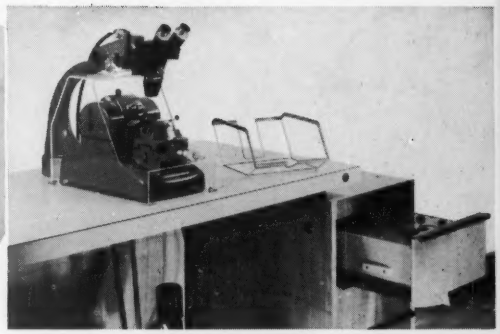

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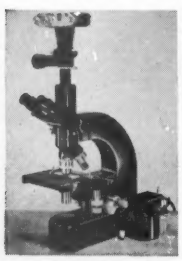

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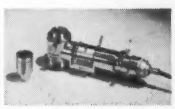

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ADVANCED OPTICS AND ELECTRONICS...SERVING SCIENCE

7 July 1961, Volume 134, Number 3471

# SCIENCE



**Cover** Columnar or comb frost on the soil in a thermal area of Yellowstone National Park, 23 February 1961. The frost was produced by the freezing of wet soil and capillary growth which raised the soil surface about 4 inches. On the day the picture was taken, the air temperature dropped to −10°F and the radiant temperature of the sky dropped to −72°F. The vertical rod is a thermometer. See page 32. [David M. Gates, Boulder Laboratories, National Bureau of Standards]

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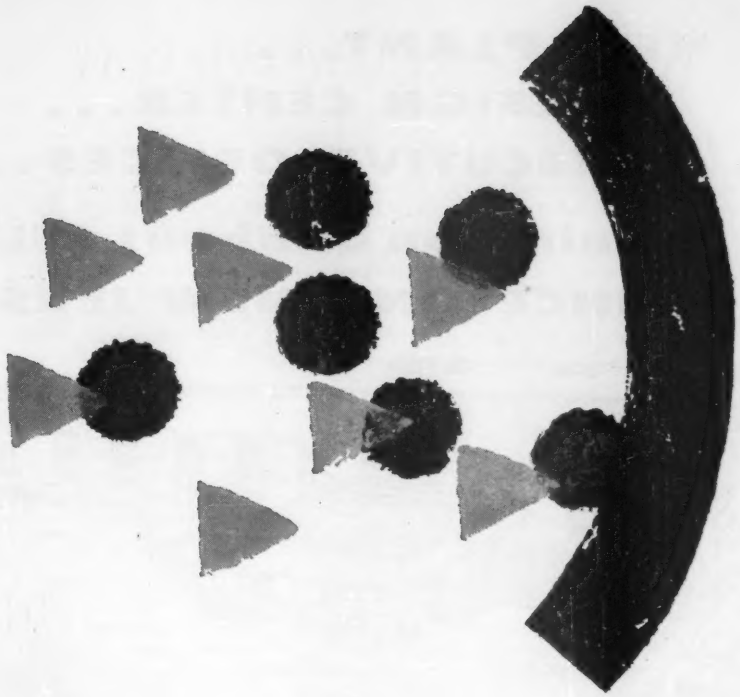

**Said Michael Faraday:** *"The amounts of different substances deposited or dissolved by the same quantity of electricity, are proportional to their chemical equivalent weights."*

Increasing requirements for pure, very thin films—especially those of ferro-magnetic elements and alloys—have become critical. To break this bottleneck, one production method under investigation is a chemical process from an aqueous solution—using metallic salts and a reducing agent.

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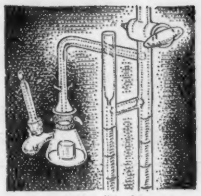
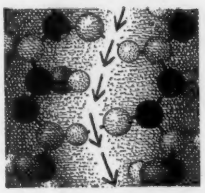
# *IT HAPPENED THIS MONTH...*

*a glance at yesterday in relation to today*



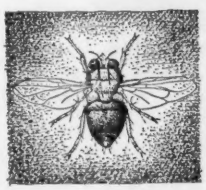
IN JULY—(1873)—Joseph Lister reviews a series of experiments supporting the germ theory of fermentation. This work utterly disproves the rival oxygen theory and shows all reported instances of spontaneous generation have been due to faulty experimentation. There is no evidence that any chemical possesses the one characteristic that distinguishes all true fermentation—self-propagation. However, it has been shown that emulsin, a peculiar albuminous principle existing in sweet and bitter almonds, can break up ten times its weight of amygdalin. "In this sense, then, as intervening between the growth of organisms and the resultant decompositions, the theory of chemical ferments might be welcomed as a valuable hypothesis."[1]

*Within a short time, this theory became fully established, and the chemical ferments elaborated by yeast became known as enzymes. It has taken considerably longer for the self-propagating properties of certain chemicals to become a major subject of research. Currently the relation of the nucleic acids to genetic duplication and virus replication has become one of the focal points of research. Whether you are concerned with enzyme action or nucleic acid chemistry, the biochemical intermediates available from Schwarz BioResearch—plain or labeled with $C^{14}$, $H^3$, $S^{35}$, or $N^{15}$—may provide useful tools for your research.*



IN JULY—(1933)—a report from the Lister Institute (London) considers the effect of proteolytic enzymes on the oxytocic hormone. Gulland and Macrae[2] find that two commercial trypsin preparations inactivate this hormone at widely different rates. A comparison experiment using quantities with equal tryptic activity clearly indicates that the inactivating enzyme is not trypsin. Nor is it a papainase, arginase, or prolinase. Aside from the fact that this inactivating enzyme accompanies proteolytic enzymes, there is no evidence adduced here that the oxytocic hormone contains peptide linkages.

*Twenty years later, du Vigneaud received the Nobel prize for investigations which established the polypeptide structure of oxytocin through amino acid analysis, systematic degradation, and chemical synthesis. Chemists at the Yeda Research and Development Company at the Weizmann Institute (Israel) have synthesized a wide variety of peptides, polyamino acids, and intermediates for peptide synthesis which are distributed by Schwarz BioResearch. A special catalog listing these compounds is available upon request. Write for a quotation on your individual requirements.*



IN JULY—(1953)—the Journal of Histochemistry and Cytochemistry discusses the function of the sarcosomes of insect flight muscle. It is suggested that these small spherical bodies play a role similar to that of mammalian mitochondria. ATP is synthesized in the sarcosomes by oxidative phosphorylation, and the energy-rich phosphate is made available for actomyosin contraction by diffusion into the adjacent muscle fibrils. Following contraction, ADP diffuses back into the sarcosomes (the sarcosomal membrane being impermeable to AMP), and the cycle is repeated.[3]

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1. Lister, J.: On the germ theory of putrefaction and other fermentative changes. Nature *8*:232 (July 17) 1873. 2. Gulland, J. M., and Macrae, T. F.: The oxytocic hormone of the posterior lobe of the pituitary gland. IV. The action of preparations of animal proteolytic enzymes, and some observations on the nature of the hormone. Biochem. J. *27*:1383, 1933. 3. Levenbook, L.: Mitochondria of insect flight muscle. J. Histochem. *1*:242 (July) 1953.

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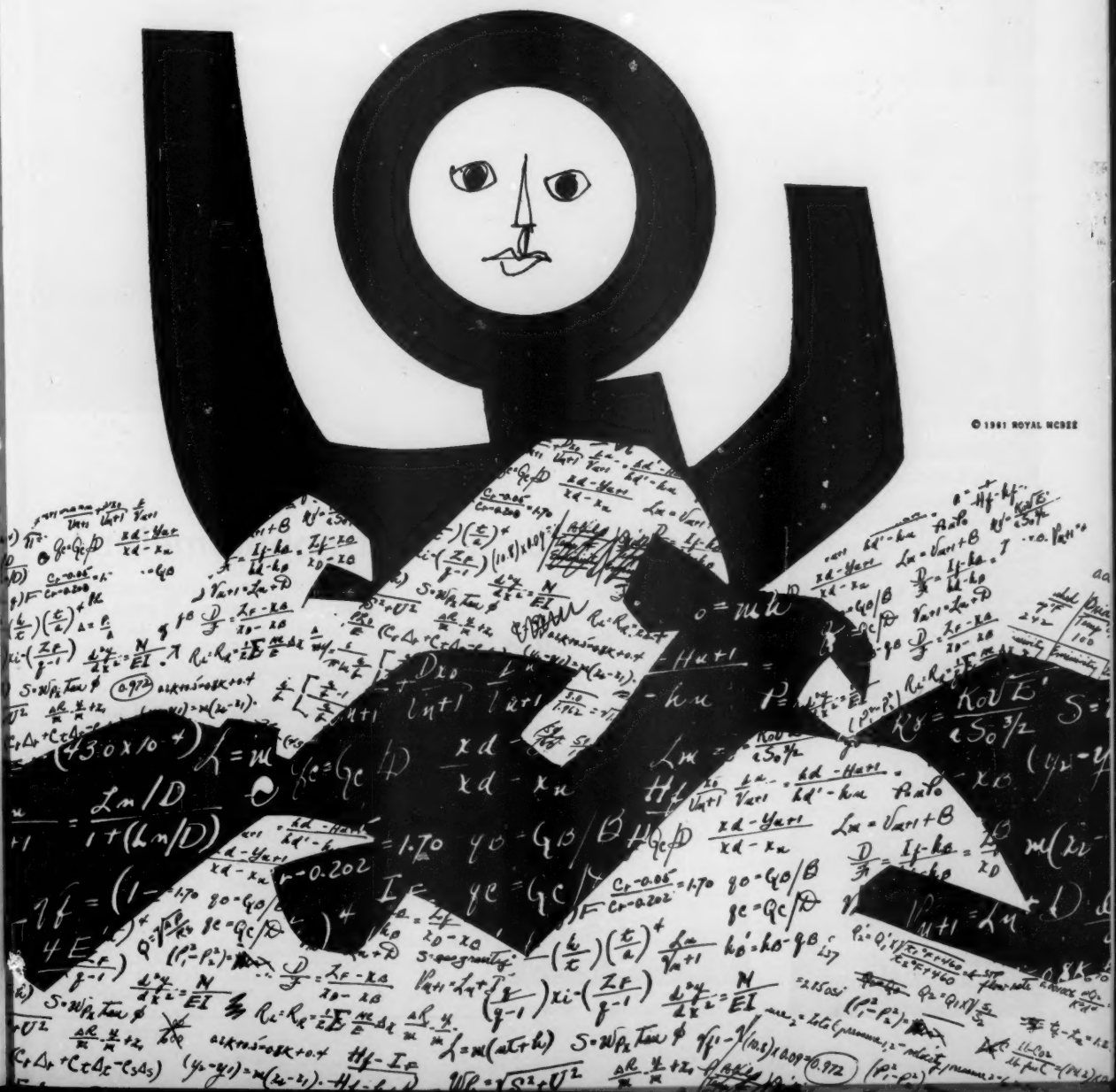

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## Two-Way Street

Atoms and molecules are the same the world over, but organisms and their interactions differ from place to place. A physicist or a chemist can do his work wherever he can find suitable equipment and adequate intellectual and financial support. Not so for the student of disease. For certain diseases—some of those characteristic of the tropics, for example—may be effectively studied only in the regions where they occur. Other diseases have been abolished in some countries; cholera is no longer endemic in the United States. One can of course study the cholera organism here in the laboratory, but the disease itself with all of its epidemiological and immunological manifestations, can only be studied elsewhere.

Despite the brilliant work that many Americans have done abroad in the medical field under the auspices of the Rockefeller Foundation or the military services or the Pan American Sanitary Bureau or the World Health Organization, we still need more skilled investigators, and there are many diseases yet to be tackled through the powerful new techniques of immunology and virology. It is in this context that the International Health and Research Act of 1960 should be viewed. The act made it possible for the Public Health Service to make funds available for the establishment of an International Center for Medical Research and Training at each of several American universities. Each center makes arrangements for one or more institutions to become affiliated with it. The centers will be permanently staffed, and staff members who do field work abroad can thus have continuing and stable careers. Upon their return to the centers they will be better equipped to train others for similar activities. The primary objectives are to give investigators opportunities for research that cannot be done in the United States and to train U.S. graduate students and postdoctoral fellows both here and abroad.

The centers and the foreign collaborating institutions are as follows: University of California and the Institute of Medical Research, Kuala Lumpur, Malaya; Tulane University and Universidad del Valle, Cali, Colombia; Johns Hopkins University and the All-India Institute of Public Health, Calcutta, and the School of Tropical Medicine, Calcutta; University of Maryland and certain institutions in East and West Pakistan; and—as announced last week—Louisiana State University and the Universidad de Costa Rica, San José.

Although the program for research and training is conceived primarily in the self-interest of the United States—after all, disease now eliminated may return, and our nationals will inevitably go where the diseases are—benefits will unquestionably flow to the collaborating countries. The effects on health should become apparent within a few years, and the presence of American investigators should help the foreign institutions to develop their own research skills.

Other and more general benefits may be expected. The knowledge gained through this research program will undoubtedly be widely applied in countries other than those directly engaged. And—although this is more remote—the procedure may well be extended to the social and behavioral sciences, perhaps through the support of private foundations. A means of helping yourself while helping others is worthy of philanthropic interest.—G.DuS.

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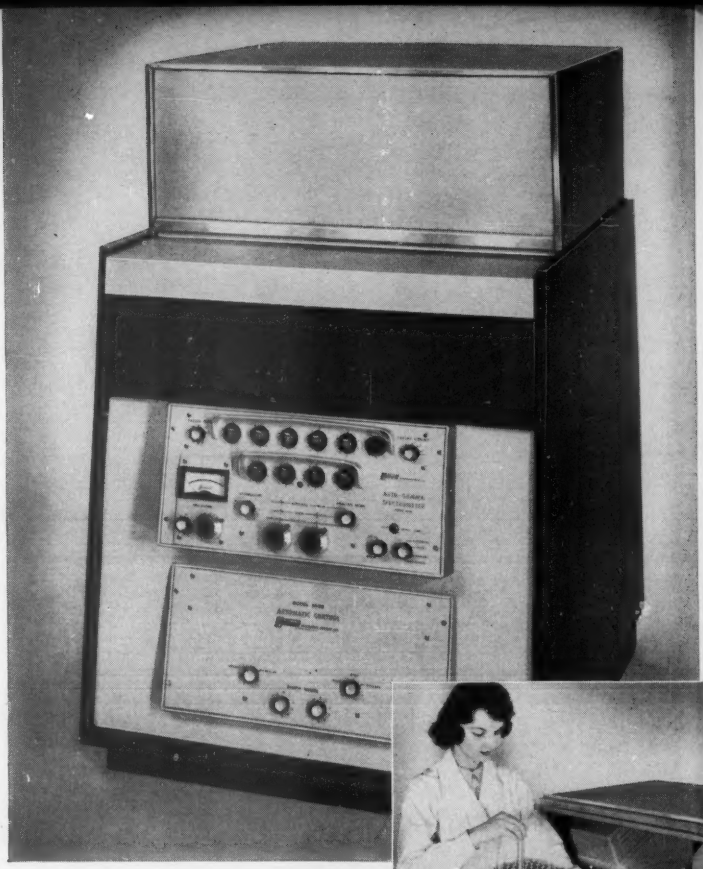



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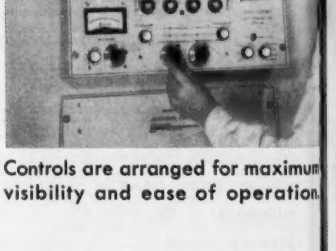

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7 July 1961, Volume 134, Number 3471 SCIENCE

CURRENT PROBLEMS IN RESEARCH

# A Molecular Theory of General Anesthesia

Anesthesia is attributed to the formation in the brain of minute hydrate crystals of the clathrate type.

Linus Pauling

During the last twenty years much progress has been made in the determination of the molecular structure of living organisms and the understanding of biological phenomena in terms of the structure of molecules and their interaction with one another. The progress that has been made in the field of molecular biology during this period has related in the main to somatic and genetic aspects of physiology, rather than to psychic. We may now have reached the time when a successful molecular attack on psychobiology, including the nature of encephalonic mechanisms, consciousness, memory, narcosis, sedation, and similar phenomena, can be initiated. As one of the steps in this attack I have formulated a rather detailed theory of general anesthesia, which is described in the following paragraphs (*1*).

It is likely that consciousness and ephemeral memory (reverberatory memory) involve electric oscillations in the brain, and that permanent memory involves a material pattern in the brain, in part inherited by the organism (instinct) and in part transferred to the material brain from the electric pattern of the ephemeral memory (*2*). The detailed natures of the electric oscillations constituting consciousness and ephemeral memory, of the molecular patterns constituting permanent memory, and of the mechanism of their interaction are not known.

The electric oscillations of the brain make themselves evident in a crude way in electroencephalograms, which show patterns of electric oscillation that depend upon the state of consciousness and the nature of the encephalonic activity of the subject. Evidence that the ephemeral memory, with an effective life that is rarely longer than a few minutes, is electrical in nature is provided by a number of observations. It has been noted that unconsciousness produced by a blow to the head or electric shock often has caused complete loss of memory of the events experienced during the period of 10 or 15 minutes before the blow or shock to the brain. Moreover, when the formation of new permanent memories is interfered with by the decreased ability of the brain to carry on metabolic processes involving proteins, as in old age or Korsakoff's syndrome (alcoholism, protein starvation, thiamine deficiency), the memory continues for a period of 10 or 15 minutes, but usually not much longer; the memory seems to persist only so long as conscious attention is directed to it (*3*).

The author is professor of chemistry, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena.

## Consciousness and Ephemeral Memory

We may discuss the electric oscillations of consciousness and ephemeral memory in terms of the exciting mechanism and the supporting structure. The supporting structure is the brain, with its neuroglial cells, neurones, and synaptic interneuronal connections that determine the detailed nature of the oscillations. The average energy of the electric oscillations may be assumed to be determined by the activity of the exciting mechanism and the impedance of the neural network. Loss of consciousness such as occurs in sleep or in narcosis (general anesthesia) may be the result either of a decrease in activity of the exciting mechanism or of an increase in impedance of the supporting network of conductors, or of both. I think that it is likely that sleep results from a decrease in the activity of the exciting mechanism, and that many sedatives, such as the barbiturates, operate by a specific action on the exciting mechanism, such as to decrease its activity; similarly, stimulants such as caffeine may have a specific action on the exciting mechanism that increases its activity. I think that general anesthetics of the non-hydrogen-bonding type, such as cyclopropane, chloroform, nitrous oxide, and 1,1,1-trifluoro-2-chloro-2-bromoethane (halothane), operate by increasing the impedance of the encephalonic network of conductors, and that this increase in impedance results from the formation in the network, presumably mainly in the synaptic regions, of hydrate microcrystals formed by crystallization of the encephalonic fluid. These hydrate microcrystals trap some of the electrically charged side-chain groups of proteins and some of the ions of the encephalonic fluid, interfering with their freedom of motion and with their contribution to the electric oscillations in such a way as to increase the impedance offered by the network to the electric waves and thus to cause the level of electrical activity of the brain to be restricted to that characteristic of

anesthesia and unconsciousness, despite the continued activity of the exciting mechanism. The formation of the hydrate microcrystals may also decrease the rate of chemical reactions by entrapping the reactant molecules and thus preventing them from coming close enough to one another to react; in particular, the catalytic activity of enzymes may be decreased by the formation of hydrate microcrystals in the neighborhood of their active sites.

### Anesthetic Agents

This theory is forced upon us by the facts about anesthesia. Hundreds of substances are known to cause general anesthesia; among them are chloroform ($CHCl_3$), halothane ($CF_3CClBrH$), nitrous oxide ($N_2O$), carbon dioxide ($CO_2$), ethylene ($C_2H_4$), cyclopropane ($C_3H_6$), sulfur hexafluoride ($SF_6$) (*4*), nitrogen ($N_2$) and argon (Ar), which under high pressure cause narcosis (*5*), and xenon (Xe) (*6*). The substances given in this list have rather similar properties as general anesthetics; these properties show a rough correlation with their physical properties, such as the vapor pressure of the liquids. Ferguson (*7*) calls them the physical anesthetics. We may infer that they function in similar ways in causing narcosis. Their chemical properties are such that it is impossible to believe that they produce narcosis by taking part in chemical reactions involving the formation and breaking of ordinary chemical bonds (covalent bonds). Moreover, although it is known that in many physiological processes the formation and rupture of hydrogen bonds play an important part, these substances, with the exception of a few (nitrous oxide, carbon dioxide, chloroform), would not be expected to form even weak hydrogen bonds, and we may call them the non-hydrogen-bonding anesthetic agents. Other narcotics, such as ethanol, may be placed in the hydrogen-bonding class.

The most surprising anesthetic agents are the noble gases, such as xenon. Xenon is completely unreactive chemically. It has no ability whatever to form ordinary chemical compounds, involving covalent or ionic bonds. The only chemical property that it has is that of taking part in the formation of clathrate crystals. In these crystals the xenon atoms occupy chambers in a framework formed by molecules that interact with one another by the formation of hydrogen bonds. The crystal of this sort of greatest interest to us is xenon hydrate, $Xe \cdot 5\frac{3}{4} H_2O$. The crystals of xenon hydrate have been shown by x-ray examination to have the same structure as those of other hydrates of small molecules, such as methane hydrate and chlorine hydrate (*8*, *9*). A thorough x-ray examination of chlorine hydrate has been made (*10*), showing that in the cubic unit of structure, with edge 11.88 A, there are 46 water molecules arranged in a framework such that each water molecule is surrounded tetrahedrally by four others, with which it forms hydrogen bonds with length 2.75 A, essentially the same as in ordinary ice (2.76 A). Whereas in ordinary ice the hydrogen-bonded framework does not contain any chambers large enough for occupancy by molecules other than those of helium or hydrogen, the framework for xenon hydrate and related hydrates contains eight chambers per cubic unit cell. Two of these chambers are defined by 20 molecules at the corners of a nearly regular pentagonal dodecahedron, and the other six are defined by 24 water molecules at the corners of a tetrakaidecahedron with 2 hexagonal faces and 12 pentagonal faces. These polyhedral chambers are illustrated in Figs. 1 and 2. The smaller chambers and the larger chambers may be occupied by the xenon atoms or methane molecules, but only the larger chambers permit occupancy by chlorine molecules, which are somewhat larger than the molecules of xenon or methane. In chlorine hydrate the dodecahedral chambers presumably are partially occupied by water molecules not forming hydrogen bonds, or, if air is present, by nitrogen molecules or oxygen molecules.

Hydrate crystals with somewhat similar structures are formed also by other anesthetic agents (*8*, *9*). Chloroform, for example, forms the hydrate $CHCl_3 \cdot 17H_2O$, which has a cubic unit of structure with the cube edge 17.30 A. The hydrogen-bonded framework of 136 molecules per cube involves 16 small chambers per cube, with the pentagonal dodecahedron as the coordination polyhedron, and 8 large chambers, each formed by 28 water molecules at the corners of a hexakaidecahedron, with 4 hexagonal faces and 12 pentagonal faces (Fig. 3). Only the large chambers can accommodate a chloroform molecule. The smaller chambers may be occupied by smaller molecules, such as xenon, which with water and chloroform forms the crystal $CHCl_3 \cdot 2Xe \cdot 17H_2O$. The volume of the 17-A

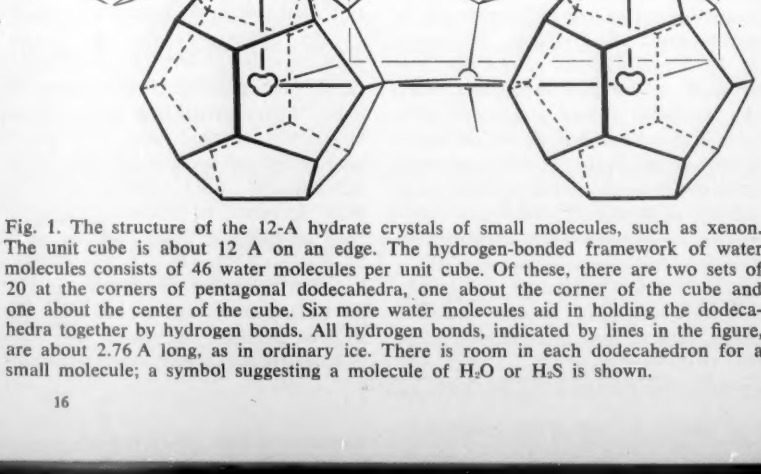

Fig. 1. The structure of the 12-A hydrate crystals of small molecules, such as xenon. The unit cube is about 12 A on an edge. The hydrogen-bonded framework of water molecules consists of 46 water molecules per unit cube. Of these, there are two sets of 20 at the corners of pentagonal dodecahedra, one about the corner of the cube and one about the center of the cube. Six more water molecules aid in holding the dodecahedra together by hydrogen bonds. All hydrogen bonds, indicated by lines in the figure, are about 2.76 A long, as in ordinary ice. There is room in each dodecahedron for a small molecule; a symbol suggesting a molecule of $H_2O$ or $H_2S$ is shown.

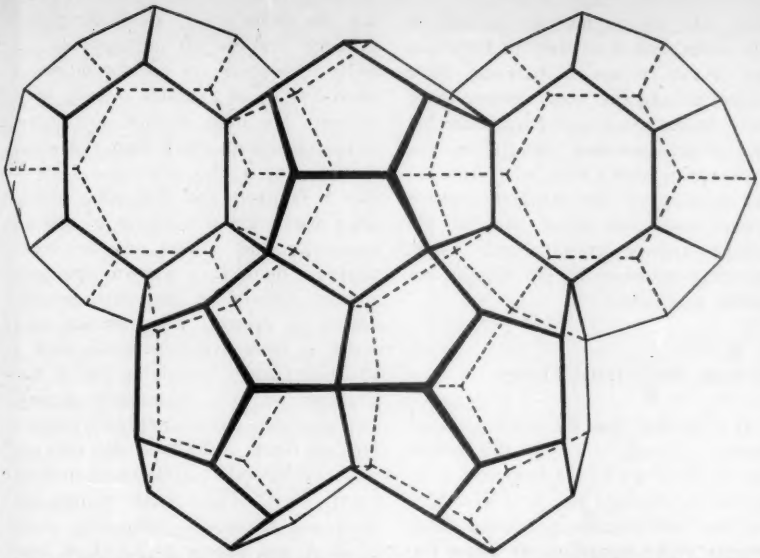

Fig. 2. Another drawing of the structure of the 12-A hydrate crystals. One dodecahedron is shown in the upper center. Around it are tetrakaidecahedra, which provide room for somewhat larger molecules than can fit in the dodecahedra. There are six tetrakaidecahedra and two dodecahedra per unit cube.

framework per water molecule is slightly larger than that of the 12-A framework—an 18-percent increase over ordinary ice (ice I), as compared with 16 percent for the 12-A framework.

The stability of the hydrate crystals results in part from the van der Waals interaction between the entrapped molecules and the water molecules of the framework and in part from the energy of the hydrogen bonds. So far as the energy of the hydrogen bonds is concerned, the stability of the framework alone would be expected to be the same as that of ordinary ice; however, the framework is more open for the hydrates than for ordinary ice, and in consequence the stabilization by van der Waals interaction of the water molecules with one another is less for the hydrate frameworks than for ordinary ice. A thorough study of experimental information about hydrate crystals by the methods of statistical mechanics, with the crystals treated as having variable occupancy of the chambers in the framework, has been carried out by van der Waals and Platteeuv; it shows that the free energy per water molecule of the empty framework is greater than that for ice I at 0°C by 0.167 kcal/mole for the 12-A framework and 0.19 kcal/mole for the 17-A framework (*11*).

The extent to which the crystals are stabilized by the van der Waals interaction of the entrapped molecules and the surrounding water molecules can be estimated by a simple calculation. The London equation for the energy of the electronic dispersion interaction between two molecules $A$ and $B$ is

$$W = -\frac{3}{2}\,\frac{\alpha_A\,\alpha_B\,E_A^{\circ}\,E_B^{\circ}}{r^6\,(E_A^{\circ}+E_B^{\circ})} \qquad (1)$$

In this equation $\alpha_A$ and $\alpha_B$ are the electric polarizabilities of the two molecules, $E_A^{\circ}$ and $E_B^{\circ}$ are their effective energies of electronic excitation, and $r$ is the distance between their centers.

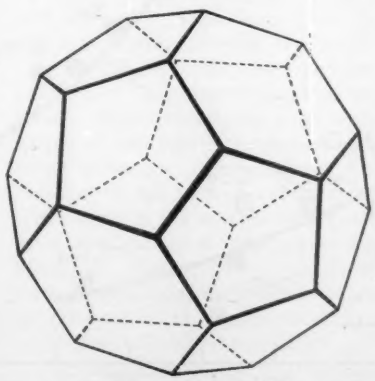

Fig. 3. The hexakaidecahedron formed by 28 water molecules in the 17-A hydrate crystals. The unit cube of these hydrate crystals, such as chloroform xenon hydrate, $CHCl_3 \cdot 2Xe \cdot 17H_2O$, contains 136 water molecules, which define 8 hexakaidecahedra and 16 dodecahedra.

It has been found that agreement between this equation and the observed enthalpies of sublimation of crystals of the noble gases is obtained by taking the effective excitation energy to be 1.57 times the first ionization energy (*12*). The first ionization energy of xenon is 280 kcal/mole, and the same value may be used for the water molecule. The interaction energy of two molecules then has the value $-aR_AR_B/r^6$, in which $R_A$ and $R_B$ are the mole refractions of $A$ and $B$, in milliliters, and $a$ is equal to 51 kcal/mole, with $r$ measured in angstroms (the mole refraction is $4\pi N/3$ times the polarizability; $N$ is Avogadro's number). In the crystal $8Xe \cdot 46H_2O$, two of the xenon molecules are in pentagonal dodecahedral chambers formed by 20 water molecules at the distance 3.85 A from the xenon atom, and the other six are in tetrakaidecahedral chambers formed by 24 water molecules, of which 12 are at 4.03 A and 12 at 4.46 A. The average energy of van der Waals attraction of a xenon atom ($R$ = 10.16 ml) with its neighboring water molecules ($R$ = 3.75 ml) is thus calculated to be −9.1 kcal/mole, which becomes −10.3 kcal/mole on addition of the similarly calculated values for the interaction with more distant water molecules and with other xenon atoms in the crystals.

The difference in enthalpy of the 12-A water framework and ordinary ice may be roughly evaluated by a similar calculation of the energy of van der Waals attraction between the water molecules (the nearest and next-nearest neighbors are at nearly the same distances in ordinary ice and the hydrate crystals, but the larger distances are different, corresponding to the more open structure of the hydrate framework). This calculation gives 0.16 kcal/mole for the 12-A framework and 0.20 kcal/mole for the 17-A framework; the close approximation of these values to the corresponding free-energy values indicates that there is little difference in entropy of the empty frameworks and ice I, as is expected from the similarity of the intermolecular forces that determine the vibrations of these hydrogen-bonded structures. The enthalpy of formation, at 0°C, of $Xe \cdot 5\frac{3}{4}H_2O$ from gaseous xenon and ice I is found by experiment (*8*) to be 8.4 kcal/mole. The value given by the foregoing calculations is $10.3 - 5.75 \times 0.16 = 9.4$ kcal/mole, minus a small correction for

the van der Waals repulsion of the xenon atoms and the surrounding water molecules. The agreement shows the extent to which the stabilization of the hydrate crystals may be understood in terms of the van der Waals interactions of the molecules.

The relation between the logarithm of the equilibrium pressure (in millimeters of mercury) of hydrate crystals and water (and also ice I) at 0°C and the mole refraction of the molecules stabilizing the hydrate crystals is shown in Fig. 4, at the left. The energy of van der Waals attraction between the water framework and the entrapped molecules is directly proportional to the mole refraction of the entrapped molecules. Hence if no other interactions affected the free energy of the hydrate crystals the points for $X \cdot 5\frac{3}{4}H_2O$ would lie on a straight line and those for $X \cdot 17H_2O$ on another straight line. There is a general concordance with this expectation, and the deviations are reasonable. For example, the molecules acetylene, ethylene, and ethane increase in size in this order, and it is likely that the van der Waals repulsion between these molecules and the water molecules of their dodecahedral and tetrakaidecahedral cages increases rapidly in this sequence in such a way as to decrease the stability of the ethylene hydrate crystal and, still more, that of the ethane hydrate crystal, with corresponding increases in the equilibrium partial pressures.

### Hydrate Microcrystal Theory

It is evident that the mechanism of narcosis cannot be simply the formation in the brain of the hydrate microcrystals $X \cdot 5\frac{3}{4}H_2O$ and $X \cdot 17H_2O$ that we have been discussing, because these crystals would not be stable under the conditions that lead to narcosis. For example, methyl chloride is narcotic for mammals at partial pressure about 0.14 atmosphere and temperature 37°C, but the crystals of its hydrate are not stable at 37° until the partial pressure reaches 40 atmospheres. In order to account for the formation of microcrystals of hydrates at body temperature we must assume that some stabilizing agent other than the anesthetic agent is also operating. I think that it is likely that the other stabilizing agents are side chains of protein molecules and solutes in the encephalonic fluid. It is known that substances resembling the charged side chains of proteins also interact with water to form hydrate crystals with a structure closely resembling that of the hydrates of the anesthetic agents. For example, tetra-*n*-butyl ammonium fluoride forms a hydrate with composition $(C_4H_9)_4NF \cdot 32H_2O$ and melting point 24.9°C. The crystals of this hydrate are tetragonal, with edge $a$ = 23.78 A and edge $c$ = 12.53 A, and with a structure that is believed to be closely similar in character to that of xenon hydrate and the related hydrates discussed above.

These crystals and similar crystals

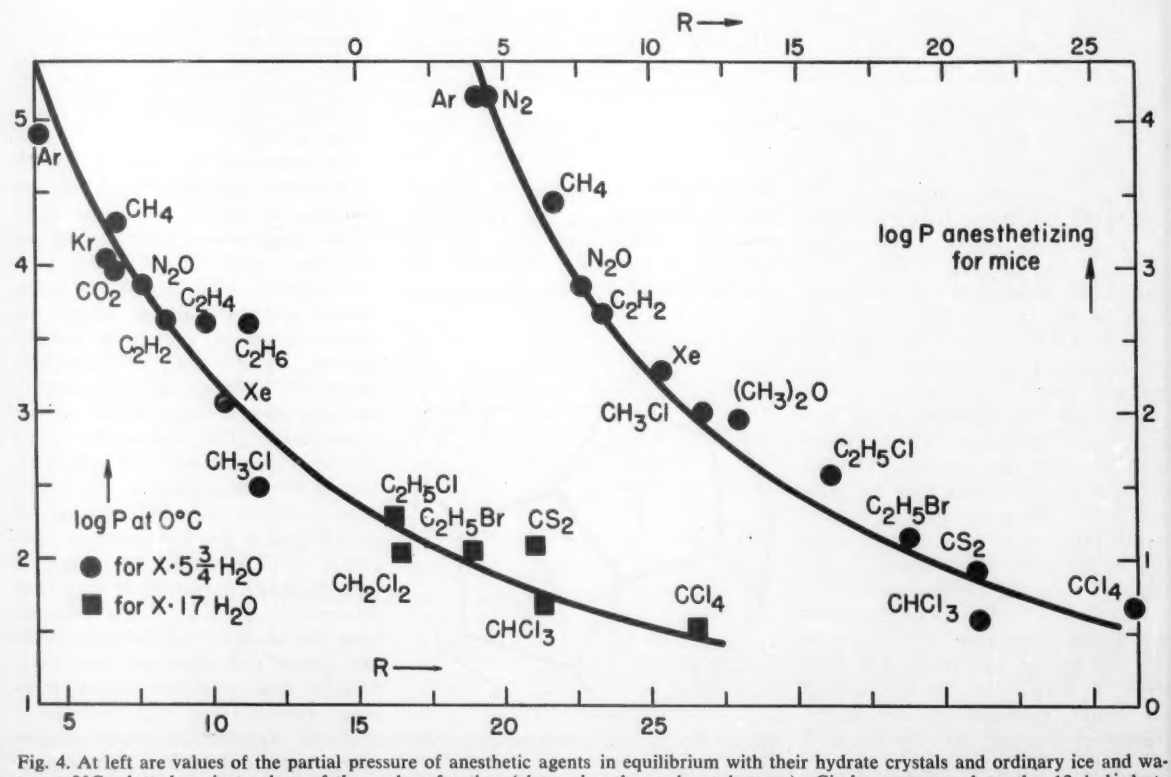


Fig. 4. At left are values of the partial pressure of anesthetic agents in equilibrium with their hydrate crystals and ordinary ice and water at 0°C, plotted against values of the mole refraction (shown by the scale at bottom). Circles correspond to the 12-A hydrate crystals; squares, to the 17-A hydrate crystals. The composition of the 12-A hydrate crystals is $X \cdot 5\frac{3}{4}H_2O$ for the smaller molecules, which can occupy both dodecahedra and tetrakaidecahedra, and $X \cdot 7\frac{2}{3}H_2O$ for the larger ones (ethane, methyl chloride), which occupy only the tetrakaidecahedra. At right the logarithm of the anesthetizing partial pressure for mice is plotted against the mole refraction of the anesthetizing agent (scale at top).

of tetra-*i*-amyl ammonium salts were first made by Fowler, Loebenstein, Pall, and Kraus (*13*). The determinations of the structure of these crystals and of related ones that they have prepared $\{[(n\text{-}C_4H_9)_3S]F \cdot 20H_2O$, $[(i\text{-}C_5H_{11})_4N]F \cdot 38H_2O$, $[(n\text{-}C_4H_9)_4P]_2WO_4 \cdot 64H_2O\}$ are being carried out by Jeffrey and his co-workers (*14*).

It is known that two anesthetic agents can cooperate to increase the stability of a hydrate framework. For example, 1 atmosphere of xenon (*15*) increases the decomposition temperature of the 17-A hydrate of chloroform by a little over 14.7°C. In the absence of xenon the crystal has the composition $CHCl_3 \cdot 17H_2O$, and in its presence $CHCl_3 \cdot 2Xe \cdot 17H_2O$. The 17-A framework forms one hexakaidecahedron and two dodecahedra per $17H_2O$; the chloroform molecules are too large to enter the dodecahedra, which can, however, be occupied by atoms of xenon or other small molecules. Similar increases of 5° to 20°C in the decomposition temperatures of 17-A hydrate crystals of $CHCl_3$, $CH_3CF_2Cl$, $CHF{=}CF_2$, $CFCl_3$, $SF_6$, and some other substances by 1 atmosphere of krypton, $H_2S$, or $H_2Se$, as well as by xenon, have also been reported (*8*, *15*). The 17-A hydrate $CHF_2CH_3 \cdot 2H_2S \cdot 17H_2O$ becomes stable in the presence of $H_2S$, whereas 1,1-difluorethane without other molecules forms a 12-A hydrate.

We may accordingly surmise that the stabilizing effect for hydrate crystals of amino acids and other solute molecules in encephalonic fluid and also of the alkyl ammonium side chains of lysyl residues and the alkyl carboxylate ion side chains of aspartate and glutamate residues, and perhaps also of certain other side chains of proteins, could operate effectively to stabilize hydrate crystals at temperatures not much lower than normal body temperature, perhaps about 25°C. The narcosis resulting from cooling of the brain, which is observed to take place at about 27°C in human beings, would then, according to our theory, be explained as resulting from the formation of these hydrate crystals in the synaptic regions of the brain and from the resultant increase in impedance of the neural network and correspondingly decreased energy of the electric oscillations. Hibernation may similarly involve the induction of unconsciousness by formation of hydrate crystals on decrease in temperature.

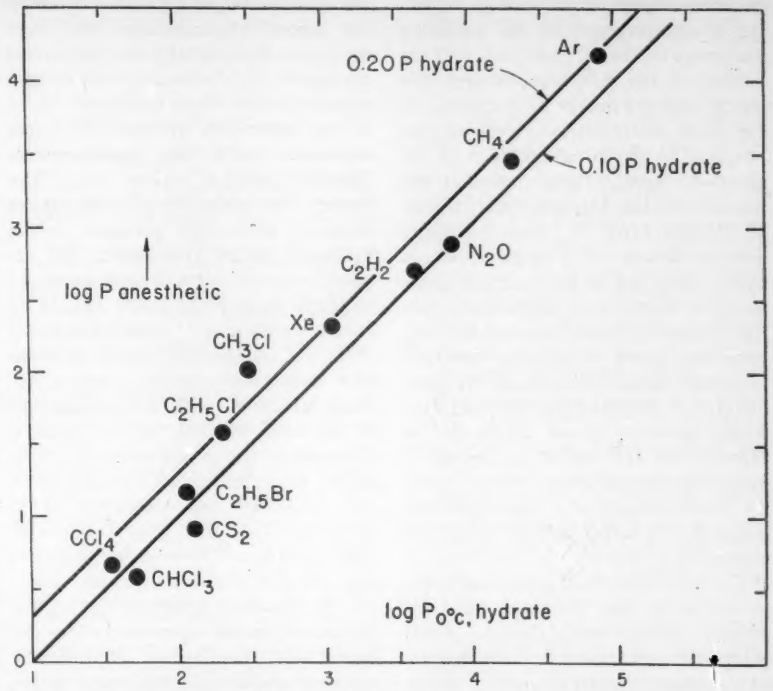


Fig. 5. A diagram showing the logarithm of the anesthetizing partial pressure of non-hydrogen-bonding anesthetic agents plotted against the equilibrium partial pressure of their hydrate crystals.

The molecules of the anesthetic agent, when present, would occupy some of the chambers in the hydrate crystal, with others occupied by the protein side chains and other groups normally present in the brain, in such a way as to give an increase in stability of the microcrystals such as to permit them to form at a temperature 10° or 15°C higher than that at which they are stable in the absence of the anesthetic agent. Through the formation of these microcrystals the conductance of the network would be decreased, with a consequent decrease in energy of the electric oscillations sufficient to cause unconsciousness. On decrease of the activity of the anesthetic agent in the encephalonic fluids, as elimination from the body takes place, the microcrystals would melt, the conductance of the synapses would be restored to its original level, and consciousness would be regained.

The logarithm of the anesthetizing partial pressure (in millimeters of mercury) for mice is shown as a function of the mole refraction of the non-hydrogen-bonding anesthetic agents in Fig. 4, at the right. The points lie close to a curve that resembles the curve for the equilibrium partial pressure of the hydrate crystals, shown at the left. The relation between the anesthetizing partial pressure and the partial pressure for the hydrate crystals at 0°C is shown in Fig. 5; the two pressures are proportional, the proportionality factor being about 0.14. The average deviation of the 11 points from the best line corresponds to the factor 1.4 (or 0.7) over a total pressure range of 4000 (for the logarithm, $\pm 0.15$ over a range of 3.6).

### Other Theories of Anesthesia

This agreement provides some support for the proposed theory, but not proof. Approximately the same correlation would be found between the anesthetizing partial pressure of the non-hydrogen-bonding anesthetic agents and any other property involving an energy of intermolecular interaction proportional to the mole refraction of the molecules. An example is the solubility in olive oil of the gaseous anesthetic agent at a standard pressure; another is the ratio of the solubility in olive oil to that in water (the oil-

water distribution coefficient). The first depends largely on the energy of van der Waals attraction of the anesthetic molecules by the oil molecules, and the second on the difference between this energy and the energy of attraction by the water molecules, and each is proportional to the mole refraction of the anesthetic agent. These quantities are involved in the Meyer-Overton theory of narcosis (*16*). The thermodynamic activity theory of Ferguson (*7*) is based upon the observed rough constancy of the ratio of anesthetizing partial pressure of non-hydrogen-bonding anesthetic agents to the vapor pressure (thermodynamic activity) of the pure liquid at a standard temperature. This rough constancy is, of course, to be expected on any theory of anesthesia involving intermolecular forces, since the vapor pressure of a liquid is determined by the forces acting between its molecules.

The lipid theories of anesthesia seem to me to be less attractive than the hydrate microcrystal theory. First, brain, like other tissues of the human body, consists largely of water: about 78 percent, as compared with about 12 percent of lipids and 8 percent of proteins. The water contains ions and proteins with electrically charged side chains and is hence expected to be largely involved in the electric oscillations that constitute consciousness; the lipids probably function mainly as insulating materials, and their electrical properties are presumably changed only slightly by the presence of nonpolar solute molecules of the non-hydrogen-bonding anesthetic agents. Moreover, the postulated change in phase from liquid to hydrate microcrystal, with a correspondingly great change in properties, provides an explanation of the large change in encephalonic activity caused by a small amount of substance, and there is no evidence to cause us to expect such a change in phase for the lipids.

## Agents That Function by Stabilization of Microcrystals

Anesthetic agents that function by the stabilization of hydrate microcrystals may be divided into several classes, determined by the sizes and shapes of their molecules. Those of the first class may be defined as having molecules sufficiently small to fit into a pentagonal dodecahedron formed by 20 hydrogen-bonded water molecules without serious van der Waals repulsion. Those of the second class include the larger molecules that are able to fit into the hexagonal tetrakaidecahedron without serious van der Waals hindrance. Those of the third class are the still larger molecules that fit into the hexakaidecahedron without serious steric hindrance. The molecules of other classes might fit into larger chambers in the hydrogen-bonded framework; for example, the tetra-*n*-butyl ammonium ion probably fits into the cavity formed by four contiguous tetrakaidecahedra about the tetrahedral position between four dodecahedra in the chlorine hydrate structure, with the elimination of the water molecule at this position, as found in the crystal-structure study of the trialkylsulfonium crystal carried out by Jeffrey and McMullan (*14*). It seems likely that several kinds of microcrystals are formed in brain tissue, and that they are variously stabilized by anesthetic agents of the several classes. It might accordingly be expected that the agents of different classes would act to some extent synergistically (and also to some extent competitively, in that molecules of an agent of one class can occupy the larger polyhedra corresponding to the succeeding classes, with, however, less stabilizing effect than for its own polyhedron because of the greater intermolecular distance). Hence it may be suggested that a mixture of agents of the dodecahedral, tetrakaidecahedral, and hexakaidecahedral classes, such as $CF_4$, $CF_3Cl$ (or $CF_3Br$), and $CFCl_3$ (or $CF_3CClBrH$), would be a better anesthetic than any one substance.

It is not unlikely that magnesium ion, $Mg(OH_2)_6^{++}$, acts as an anesthetic agent by stabilizing hydrate microcrystals. This ion, with its attached water molecules, would become a part of the hydrogen-bonded framework. Molecules such as ethanol and tribromoethanol, $CBr_3CH_2OH$, may be expected to participate in the formation of microcrystals of hydrates in such a way that the molecule becomes a part of the hydrogen-bonded framework and also has a space-filling and van der Waals stabilizing effect. Other hydrogen-bond-forming narcotic agents may attach themselves by the formation of hydrogen bonds to protein molecules in a specific way so as to interfere specifically with certain encephalonic processes. The study of these specific effects will require the detailed investigation of the proteins and other substances present in brain and nerve tissue.

## Related Studies

Many experiments by means of which evidence about the proposed molecular theory of anesthesia may be obtained are suggested by the theory; some of them are being carried out in our laboratories. Studies of crystalline hydrate phases formed in the presence of anesthetic agents, ions, and protein molecules or molecules and ions similar to protein side chains might yield interesting results.

The "iceberg" theory of ionic solutions (*17*) and of hydration of proteins (*18*) is closely related to the hydrate microcrystal theory of anesthesia; the only change suggested for these theories is that the ordered arrangement of water molecules about the solute ions and protein side chains has one or another of the clathrate structures rather than the more compact ice-I structure.

The hydrate microcrystal theory of anesthesia clearly suggests that the anesthetic agents should act on all tissues, and not just on brain and nerve tissue. It was pointed out nearly a century ago by Claude Bernard (*19*) that "an anesthetic agent is not just a special poison of the nervous system; it anesthesizes all elements, all tissues by numbing them, temporarily blocking their irritability." Many studies of the effects of anesthetic agents on physiological processes other than thinking have been reported (*20*).

At present there is little information available about the fraction of the aqueous phase in the brain that is changed into hydrate microcrystals during anesthesia, or about the dimensions of the microcrystals. Experiments now under way should provide some information. The results of density-gradient ultracentrifuge studies of solutions of deoxyribonucleic acid by Hearst and Vinograd (*21*) indicate that at 25°C the nucleic acid molecules have about 50 water molecules of hydration per nucleotide residue at water activity near unity. This suggests that the microcrystals have linear dimensions of about 20 A or 30 A (for nucleic acid, of course, they continue along the Watson-Crick double helix). A hydrate cube with edge 30A contains about 750 water molecules.

## Conclusion

The hydrate-microcrystal theory of anesthesia by non-hydrogen-bonding agents differs from most earlier theories in that it involves primarily the interaction of the molecules of the anesthetic agent with water molecules in the brain, rather than with molecules of lipids. The postulated formation of hydrate microcrystals similar in structure to known hydrate crystals of chloroform, xenon, and other anesthetic agents as well as of the substances related to protein side chains, entrapping ions and electrically charged side chains of protein molecules in such a way as to decrease the energy of electric oscillations in the brain, provides a rational explanation of the effect of the anesthetic agents in causing loss of consciousness. The striking correlation between the narcotizing partial pressure of the anesthetic agents and the partial pressure necessary to cause formation of hydrate crystals provides some support for the proposed theory, but it is recognized that any theory based upon the van der Waals attraction of the molecules of the anesthetic agent for other molecules would show a similar correlation, inasmuch as the energy of intermolecular attraction is approximately proportional to the polarizability (mole refraction) of the molecules of the anesthetic agent. The proposed theory is sufficiently detailed to permit many predictions to be made about the effect of anesthetic agents in changing the properties of brain tissue and other substances, and it should be possible to carry out experiments that will disprove the theory or provide substantiation for it.

### References and Notes


1. The work reported in this article (contribution No. 2697) is part of a program of investigation of the chemical basis of mental disease supported by grants to the California Institute of Technology made by the Ford Foundation and the National Institutes of Health. This theory has been presented in lectures at Pacific State Hospital, California State Department of Mental Hygiene, Spadra (23 May 1960); at a meeting of the Western Society of University Anesthetists, Stanford Medical School, Palo Alto, Calif. (21 Jan. 1961); at a meeting of the Hawaii section of the American Chemical Society and Sigma Pi Sigma, University of Hawaii, Honolulu (5 Apr. 1961); and at a meeting of the Mediterranean section of the Société de Chimie Physique, Toulouse, France (25 Apr. 1961).
2. L. A. Jeffress, Ed., *Cerebral Mechanisms in Behavior* (Wiley, New York, 1951), especially sections by W. S. McCulloch. McCulloch (p. 101) suggests that there are three kinds of memory: (i) reverberatory memory; (ii) a kind of alteration of the nervous net with use; and (iii) a storage memory with a bottleneck both in putting information in and in taking it out. If the second and third are to be differentiated at all, I think that they may be classed together as involving permanent or semipermanent molecular patterns.
3. McCulloch (*2*, p. 58) has reported an example of a man over 80 years old, and with no power of adding to his permanent memory, who held all the details of an important meeting of a board of directors in his mind during the 8 hours of its duration, so that he was able to summarize it brilliantly during the last half hour of the meeting; yet a few minutes after the meeting he had forgotten it completely and permanently.
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# Drugs in the Brain

## Autoradiography and radioassay techniques permit analysis of penetration by labeled drugs.

Lloyd J. Roth and Charles F. Barlow

The brain has been a source of continuing interest and investigation throughout recorded history. It has been studied by anatomists, physiologists, biochemists, and psychologists and, in its response to drugs, by pharmacologists. The multiple-disciplinary approach has not only revealed the magnificent organization and infinite complexity of the brain but has constantly stimulated investigators to extend their knowledge of its structure and function. The enormous degree of structural differentiation in the brain is obvious on gross inspection, and examination by light and electron microscopy reveals wide variety in structure and arrangement at the cellular and subcellular level. The amount of blood flowing through the various anatomical subdivisions of the brain is neither uniform nor constant. More blood flows through gray matter than through white, the effects of physiologically controlled changes in blood flow being disproportionate for the two types of tissue.

In addition, evidence has accumulated to demonstrate a regional biochemical topography in brain for both enzyme and substrate. Enzyme activity clearly varies in different regions. For example, levels of acetylcholine esterase may differ from one region to another by a factor of 50, whereas levels in the same regions of similar species may be remarkably constant (*1*). The histological complexity of the brain led Lowry *et al.* to develop elegant microbiochemical techniques for analysis of brain samples as small as 1 microgram (*2*). Robins *et al.* utilized these methods in mapping the concentrations of as many as nine enzymes (*3*). They were able to demonstrate finite differences in concentration in such subdivisions as the outer layers of the cerebral and cerebellar cortex. The concentrations of endogenous, active substances have also been found to vary with the brain region examined. Concentrations of noradrenaline have been found to be highest in the hypothalamus and the area postrema (*4*). Serotonin is highly localized; structures of the limbic system contain distinctly more serotonin than the neocortex (*5*).

Studies with exogenous substances, such as drugs, frequently ignore the specific and potentially unique response of the functionally specialized tissues in discrete anatomic loci of the brain. Specificity has been shown in the monkey at the gross level with certain 8-aminoquinolines (*6, 7*) which are striking in their ability to produce structural changes within selected anatomical areas of the brain (Fig. 1). Certain arsenical compounds have also been found to produce specific necrotizing lesions in the lateral geniculate bodies of monkeys (*8*). Marked changes in the monkey brain have been noted after poisoning with methyl alcohol, necrosis and hemorrhage being produced in the putamen and caudate nucleus (*9*). Carbon disulfide produces a specific bilateral degeneration of the globus pallidus and substantia nigra which is not related to vascular damage (*10*). What, then, are the determinants which govern such localized destructive lesions? No answers are available, yet these examples suggest that certain specific relationships exist between tissue and toxin. Richter has commented (*7*) that it is "difficult to escape the conclusion that there is some specific selective affinity, chemically direct or indirect, between the toxin and the chemical organization of the part of the brain destroyed."

These extreme examples of localized necrotizing action on specialized nervous tissue raise certain questions about any drug which affects the central nervous system. Is the action on nervous tissue per se, or does the drug produce a response in the brain by some secondary effect? If a drug enters the brain, what factors determine the entry, into what structures does it move most readily, and where does it concentrate? The question should be asked, Do localized concentrations of a drug have significance only in relation to regional brain characteristics or do they, in addition, have pharmacological significance?

The problem of entry and concentration of drugs in brain loci is often sidestepped, although the blood-brain barrier is frequently cited to explain a series of pharmacological reactions which are not otherwise understood. Nor is the barrier itself uniform throughout the brain. It is poorly established in the area postrema, the periventricular nucleus, the supraoptic nucleus, the pituitary, and the pineal body. The blood-brain barrier appears to be a combination of factors, including capillary endothelium, surrounding glial cells, and perhaps other anatomical components, all of which may bar or admit drugs to the brain parenchyma.

Analyses of drugs in whole brain or whole-brain homogenates, while important first steps, may actually obscure subtle variations of correlative value. It is important, therefore, to measure drug concentration in discrete areas of the brain with respect to time after administration, and to explore the possible influences of such factors as disease and maturational, nutritional, physiological, and biochemical states.

Techniques are presently available which can assist in elucidating the problem of entry of drugs into the brain and its structural subdivisions, under conditions in which pharmacological levels of a drug are employed. The techniques of autoradiography and radiochemical assay offer means for studying this problem, through utilization of animals given low or trace levels of active substances. Autoradiography provides an especially valuable integrated visual description of penetration and localization phenomena in discrete anatomic loci and also provides a qualitative comparison of content from structure to structure. Thus, relative changes between areas may be related to time after administration as

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well as to developmental age and physiologic or pathologic state (*11*).

We have found that drugs that are classified together because of similar basic chemical structures, such as the barbiturates, may have profoundly different penetration patterns. No definitive generalizations can be made until more specific and detailed information is obtained on many more compounds. We give here a brief summary of our work on the penetration of cat brain by a number of synthetically labeled substances, and a discussion of some of the factors which influence penetration and localization. We refer to the methodology of other workers by citation. A brief description of the technique we have utilized is given below (*12*).

### Factors Influencing Entry into Brain

*The circulation.* The brain possesses few metabolic reserves, and a substantial flow of nutrient and oxygen (20 percent of the total oxygen consumption of the body) must be supplied to it. Because of the large amount of blood that circulates through the brain [54 $cm^3$ per 100 g per minute in adult man (*13*)], it is tempting to assume that the penetration of drugs into its parenchyma may be related directly to the quantity of blood supplied. Such assumptions ignore the minute amounts of exogenous substances usually accepted by the brain in spite of the fact that approximately 15 percent of the total blood flow passes through the brain. Because of the importance of the cerebral circulation in the metabolic functions of the brain, many attempts have been made, with both anatomical and physiological techniques, to estimate how much blood is supplied to the various subdivisions of cat brain. In general, dynamic studies have been limited to structures, such as the pial vessels, which can be easily exposed. Capillary counting and extrapolation of data have served for describing the circulation of the deeper structures. The entire problem is complicated by the geometry of the brain and its enclosure within the bony skull.

The techniques of autoradiography and densitometric assay have been successfully applied by Kety, by Sokoloff, and by their co-workers (*14, 15*) in the development of a method capable of providing data on blood flow in selected regions of the cat brain. These workers infused the radioactive gas trifluoroiodomethane and froze the head in liquid nitrogen after decapitation. They were able to measure blood flow in 28 regions of the brain and cord and demonstrated a striking nonuniformity of flow among structures of the adult cat brain. They found that gray matter was more vascular than white matter, and that the colliculi and the lateral and medial geniculate bodies, as well as the cerebral cortex, were among the regions of most active blood flow. These variations are shown in the autoradiogram reproduced in Fig. 2.

We have supplemented the data of these workers, utilizing iodine-131 serum albumin (RISA, Abbott) to demonstrate the relative vascularity of various areas of the cat brain. Autoradiography and densitometric measurement of the exposed film gave values for static vascularity that were in good agreement with those obtained

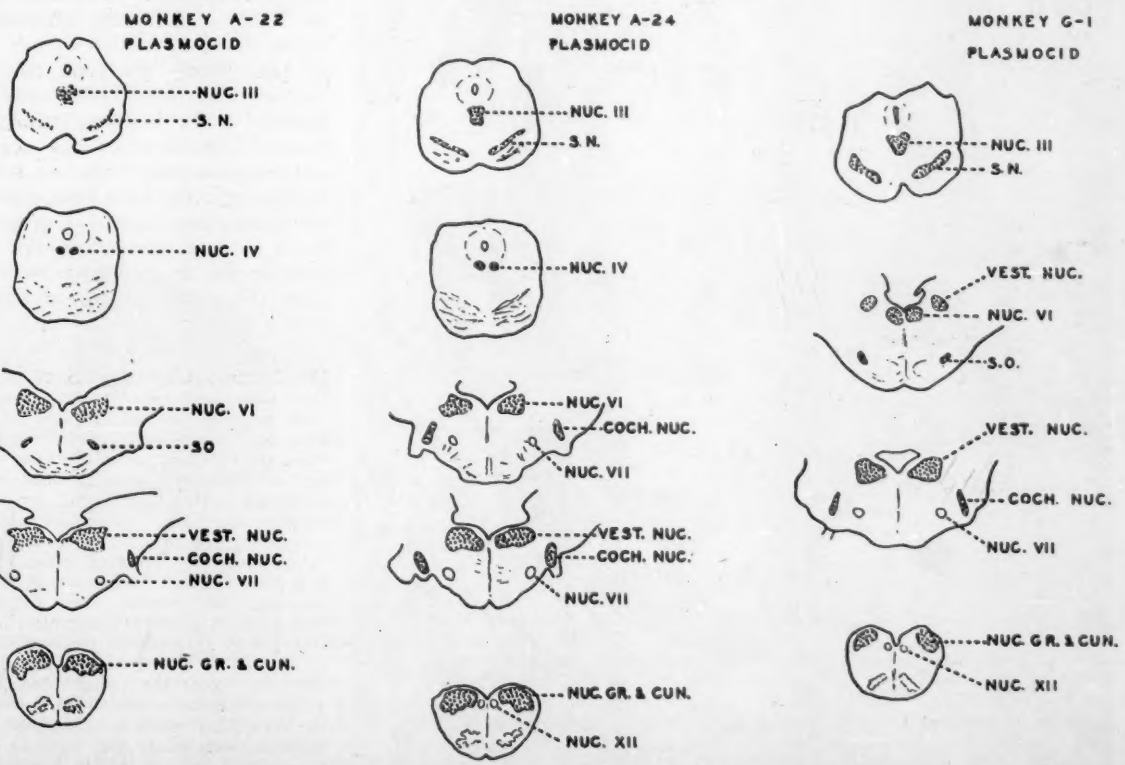
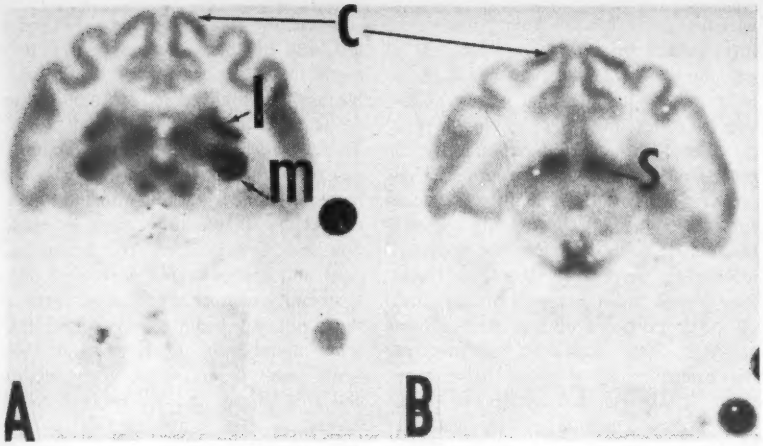
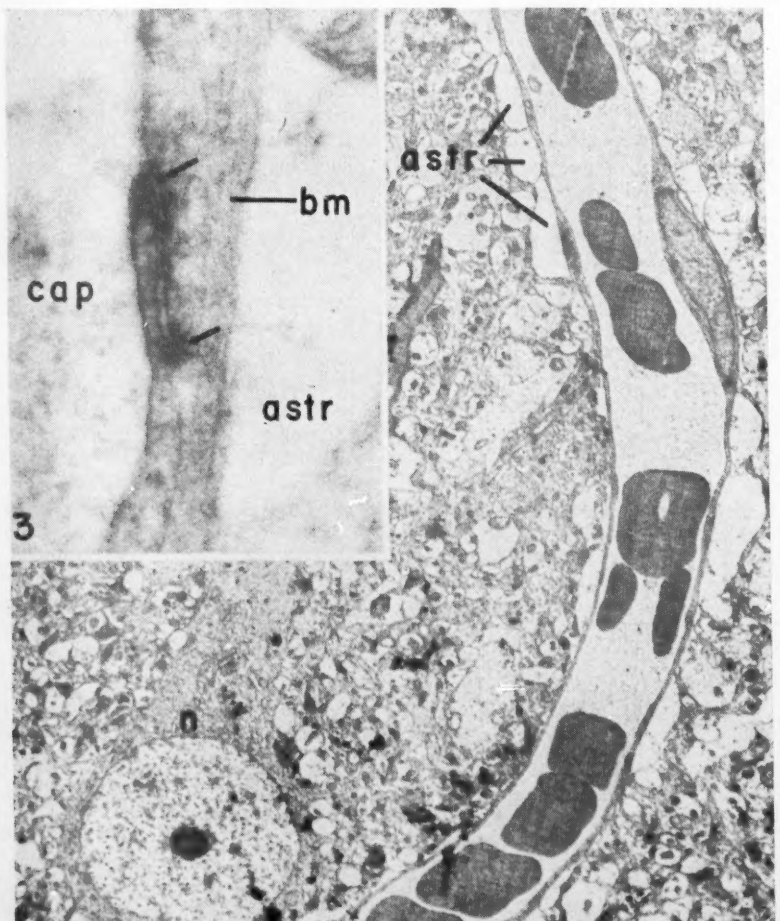



Fig. 1. Projection drawings from serial sections, showing the distribution of necrotizing lesions in the brain-stem nuclei of plasmocid-treated monkeys. [From R. B. Richter, *J. Neuropathol. Exptl. Neurol.* 8, 155 (1949)]




previously by capillary-counting techniques and re-emphasized the abundant vascularity of geniculates and colliculi (*16*).

Detailed determination of blood flow and vascularity for the brains of immature cats has not been reported, although each of the afore-mentioned techniques should be applicable. Measurements of blood flow and vascularity are germane to the question, Does local circulation constitute a major determinant in the penetration and concentration of drugs in the central nervous system? Before reporting our findings on these relationships, we discuss briefly certain other characteristics of brain which may also play a role in influencing drug penetration.

*Solute spaces.* Electron-microscopic studies reveal that there is very little extracellular space in the brain, and that the membranes of cellular elements are in intimate contact with each other and with the capillaries (*17*). Maynard *et al.* (*18*) report that brain capillaries have a unique, thick, and solid arrangement of endothelial cells, the pericapillary structure being composed largely of astrocyte feet applied directly to the capillary wall. Maynard and her co-workers have also shown that the extracellular spaces found by earlier workers are, in fact, watery glia, and that the capillary endothelium is in close apposition to the basement membrane. Figure 3 demonstrates this concept and indicates what, with less refined techniques, could have been mistaken for extracellular spaces. Calculations based on the assumption that the chloride ion is entirely extracellular show this chloride space to account

Fig. 2 (top). Autoradiograms of coronal slices of cat brain, showing regional variations in blood flow as indicated by distribution of $I^{131}$-labeled trifluoroiodomethane, an inert gas. Areas of greater density are areas of greater blood flow. *c*, striate cortex; *l*, lateral geniculate ganglia; *m*, medial geniculate ganglia; *s*, superior colliculi. [From L. Sokoloff, "Local blood flow in neural tissue," chap. 6 in *New Research Techniques of Neuroanatomy*, W. Windle, Ed. (Thomas, Springfield, Ill., 1957) (anatomical labels ours)]. Fig. 3 (bottom). Electron photomicrograph of the cerebral cortex of an adult rat. Note the virtual absence of visible extracellular space. *cap*, lumen of the vessel; *astr*, astrocytic cytoplasm; *bm*, basement membrane; *pvc*, flattened perivascular cell; *n*, large neuron. [From E. A. Maynard, R. L. Schultz, D. C. Pease, *Am. J. Anat.* **100**, 409 (1957), plate 2]

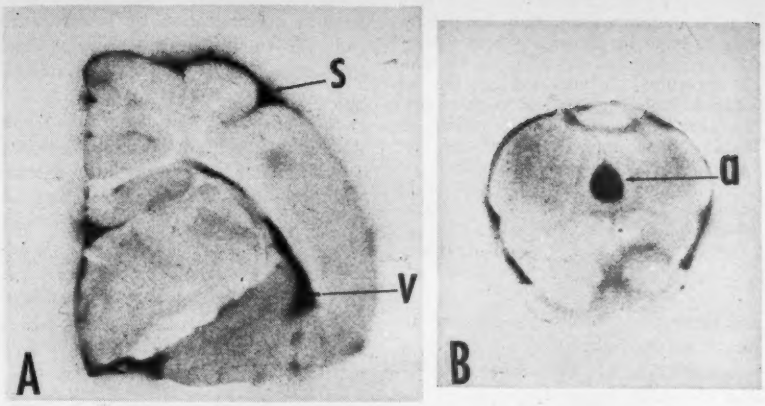



Fig. 4. Autoradiograms of the cerebral hemisphere (*A*) and midbrain (*B*) of a cat 4 hours after injection of $S^{35}$-labeled sodium sulfate. Cerebrospinal fluid is shown by the heavy radiodensity in subarachnoid spaces (*S*), ventricles (*V*), and aqueduct of Sylvius (*a*). The fluid is sharply confined by the anatomical boundaries of these structures. Anatomical structures within the brain show almost equal radiodensities. [From L. J. Roth, J. C. Schoolar, C. F. Barlow, *J. Pharmacol. Exptl. Therap.* **125**, 128 (1959)]

for 30 percent of the weight of brain. Experiments in which $S^{35}$-labeled sulfate (*19*), inulin (*20*) and sucrose (*21*) were used as indicators of extracellular spaces yielded values more in line with the electron-microscopic findings.

Using the autoradiographic and radioassay techniques and $S^{35}$-labeled sulfate as an extracellular indicator, we have re-examined this problem in cats, utilizing ureter ligation to maintain a near-plateau concentration of sulfate in plasma (*22*). This resulted in a constant level in brain between 4 and 8 hours after administration. At this time the concentration of sulfur-35 is of the same magnitude (2.5 to 3.8 percent) in all regions; correction for metabolic incorporation alters these percentages very little.

The autoradiograms (Fig. 4) support the tissue assay data and show little distinction in level among anatomical structures and no relation to variations in vascularity or blood flow. The area postrema is the only parenchymal region of high autoradiographic density, while the cerebrospinal fluid in subarachnoid spaces and in the ventricular system is also prominent. The sharp line of demarcation between the brain parenchyma, together with the high autoradiographic density of cerebrospinal fluid, indicates that the higher concentration of sulfate is sharply confined within the boundaries of the subarachnoid space. It also illustrates the superiority of the autoradiographic technique in elucidating such phenomena.

Thus, the extracellular space previously thought of as bathing the cellular elements of the brain is found, by these physiological indicators, as well as by the electron microscope, to be very small. It is possible that the small extracellular space in the brain of adult cats is a significant factor affecting the entry and accumulation of certain substances in the brain. We have extended our observation on the sulfate space to the immature kitten, and some of our findings have differed strikingly from findings in the adult animal. The sulfate space is appreciably greater in the first month of life and, in addition, marked regional differences are observed (Fig. 5*B*).

Urea has been used frequently as a measure of the total body water because of its presumed easy access to all fluid compartments of the body

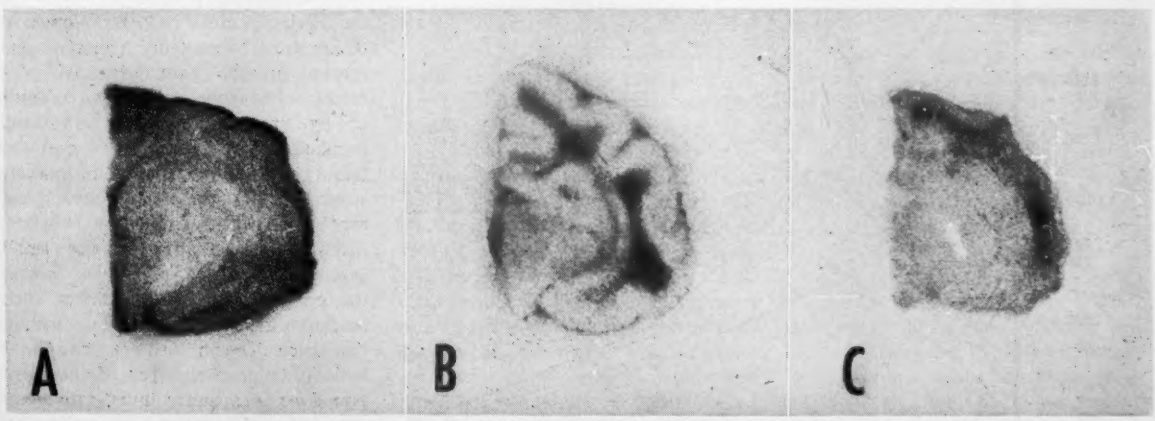



Fig. 5. Autoradiograms of cerebral hemispheres of newborn kittens. (*A*) Hemisphere 1 hour after injection of $C^{14}$-labeled urea, showing equal radiodensities in the cerebral cortex and in white matter, a finding that correlates well with the findings that these structures have equal water content and that significant amounts of myelin in white matter are lacking. [From J. C. Schoolar, C. F. Barlow, L. J. Roth, *J. Neuropathol. Exptl. Neurol.* **19**, 216 (1960)] (*B*) Hemisphere 6 hours after injection of $S^{35}$-labeled sulfate, showing greater radiodensity in primordial white matter than is found in the adult animal (Fig. 3). At 6 hours the sulfate space (after correction has been made for metabolic incorporation of sulfur-35 in plasma and brain) accounts for 16.8 percent of the weight of the cerebral cortex and 33.5 percent of that of the cerebral white matter, as compared to values of slightly less than 4 percent in adult animals. [From C. F. Barlow, N. S. Domek, M. A. Goldberg, L. J. Roth, *A.M.A. Arch. Neurol.*, in press] (*C*) Autoradiogram of hemisphere after injection of $C^{14}$-labeled phenobarbital, showing the greater density in primordial white matter. [From N. S. Domek, C. F. Barlow, L. J. Roth, *J. Pharmacol. Exptl. Therap.* **130**, 285 (1960)]

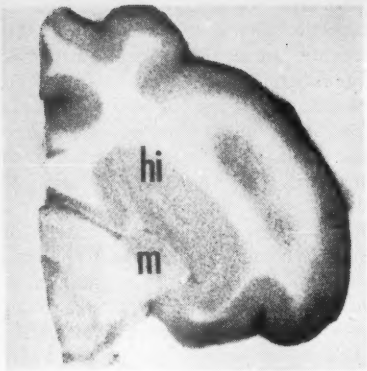



Fig. 6. Autoradiogram showing penetration of brain by $C^{14}$-labeled urea 6 hours after injection and definition of anatomical structure, as indicated on the developed film. The cerebral cortex shows the highest radioactivity; white matter, the lowest. Hippocampus (*hi*) and the very vascular medial geniculate body (*m*) show intermediate activity. [From J. C. Schoolar, C. F. Barlow, L. J. Roth, *J. Neuropathol. Exptl. Neurol.* **19**, 216 (1960)]

(*23*). We have, therefore, utilized $C^{14}$-labeled urea as an indicator of the behavior of a substance which would be expected to enter all the extra- and intracellular water of brain tissue. For this purpose urea has the advantages of being nonionic, water-soluble, and presumably not significantly metabolized by brain, and of having little or no tendency to bind to plasma or tissue protein. Autoradiograms and radioassay of dissected areas of the cat brain, after a single injection of $C^{14}$-labeled urea in trace amounts, clearly indicate a nonuniform penetration pattern, with maximum levels in brain and cerebrospinal fluid not attained before 6 hours. Furthermore, the rate of penetration into gray matter exceeds that for white matter (Figs. 6 and 7). It seems likely that regional difference with respect to penetration is related to the barrier posed by the multiple membranes of the numerous laminated myelin sheaths that are found in white matter (Fig. 8). This concept is supported by our observation of equal rate of entry into cortex and white matter of the newborn kitten (Fig. 5*A*). At this age the total water contents of cortex and of white matter are similar, and myelin has not yet developed. It would appear that vascularity and blood flow play a minor role in urea penetration, since regions of high vascularity, such as the colliculi and geniculate bodies, contain a smaller concentration of labeled urea than the equally or less vascular cerebral cortex at all times after administration (*24*).

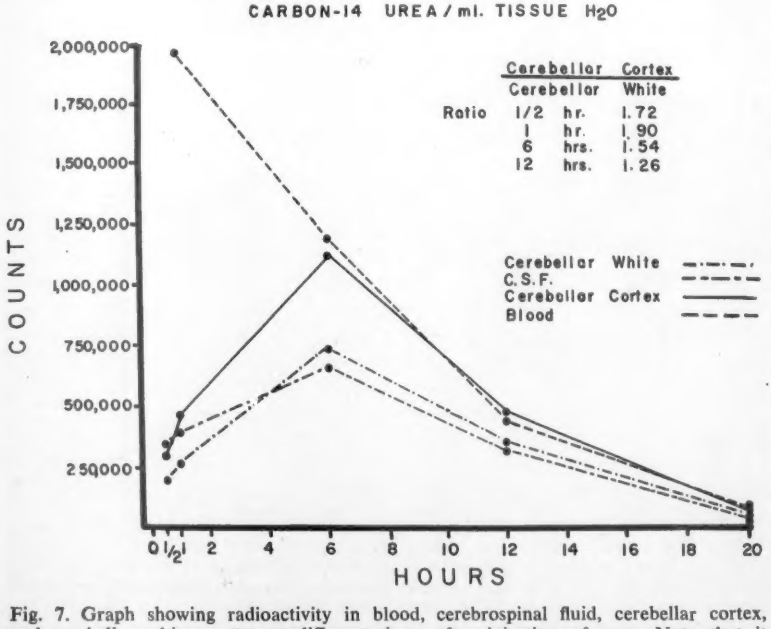



**Fig. 7. Graph showing radioactivity in blood, cerebrospinal fluid, cerebellar cortex, and cerebellar white matter at different times after injection of urea. Note that it requires 6 hours for the level of activity in the cerebellar cortex to approach that in blood, and that the urea enters white matter more slowly and perhaps less completely. [From J. C. Schoolar, C. F. Barlow, L. J. Roth, *J. Neuropathol. Exptl. Neurol.* 19, 216 (1960)]**

*Blood-brain barrier.* There can be no doubt that the brain possesses a unique and specialized mechanism for excluding many substances presented to it by the circulation. The brain may exclude certain compounds completely, or admit them in only small amounts, while other organs become easily saturated.

The anatomical and physiological nature of the blood-brain barrier is a matter for active research and discussion. Some view the barrier as lying between the circulating plasma within the capillaries and the extracellular fluid (*25*), while others think the capillary endothelium (*26*) or the perivascular glia (*27*) constitute the barrier. The watery constitution of these glial cells, which fill the interstices in the neuropil, in no way detracts from their potential importance in controlling exchange between capillaries and neurons. The nature of the barrier differs in the various regions of the brain, such as areas of gray matter, areas of white matter, and choroid plexus. Substances normally excluded from the brain may penetrate the parenchyma readily if injected directly into the ventricles (*28*). Feldberg and Fleischhauer have shown that this may be an active process, since bromphenol blue failed to penetrate from the cerebrospinal fluid in the nonliving cat, whereas it penetrated deeply in the living animal (*29*). We have demonstrated repeatedly a marked difference in the penetration of gray matter and white by drugs, as well as by urea and sulfate, and have ascribed this difference in part to the lipoid lamellae of the white matter, suggesting an additional anatomical aspect of the blood-brain barrier. Moreover, boundaries of the small extracellular space probably restrict the entry of certain substances such as inulin, sucrose, and sulfate ion to that space. The physical (*30*) and metabolic (*31*) characteristics of the compound or ions under investigation are also influential factors in controlling penetration. Alteration in penetration may also be influenced by the inhalation of carbon dioxide, with concomitant variations in acid-base balance (*32–34*).

Nor can the age of the animal be ignored, since degree of myelinization, water content of various anatomical

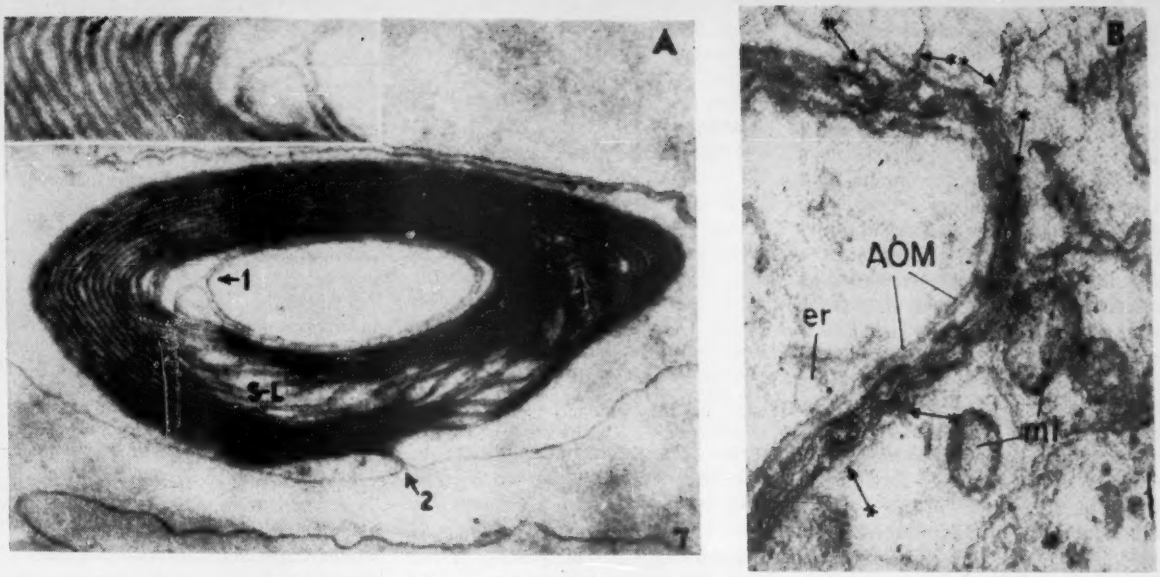



Fig. 8. Electron photomicrographs showing the laminated membranes characteristic of myelin sheaths of the peripheral (*A*) and the central (*B*) nervous systems. [*A*, from J. D. Robertson, *J. Biophys. Biochem. Cytol.* **4**, 349 (1958); *B*, from E. DeRobertis, H. M. Gerschenfeld, F. Wald, *ibid.* **4**, 651 (1958)]

divisions, cellular architecture, and biochemical organization of the brain vary with the degree of maturity (*31*). Each of these factors may profoundly influence the development of barriers and fluid spaces, and thus they may alter the penetrability of different structures in dissimilar ways. Our studies of penetration of kitten brain by $C^{14}$-labeled phenobarbital (*35*), $C^{14}$-labeled urea (*29*), and $S^{35}$-labeled sulfate (*22*) clearly demonstrate these differences (Fig. 5).

In view of the foregoing observations, it would appear that a whole series of anatomical, physiological, biochemical, and maturational factors, all unique to brain and many of them showing regional variation, must be taken into account in interpreting barrier phenomena. Herlin states (*36*): "It is practical to include in the term 'barrier' all the phenomena which prevent, reduce, delay, or even actually facilitate the penetration of a substance into the CNS [central nervous system]. The penetration might occur by dialysis, ultrafiltration, osmosis, the Donnan equilibrium, electrical charges, lipoid solubility, special tissue affinity or metabolic activity. A more limited definition of this term would imply a more exact knowledge of the barrier mechanism than one really possesses. If one had such exact knowledge, it would be unnecessary to use the term 'barrier'. It would be preferable to describe what happens. In reality, the barrier mechanisms may be different for each substance." These statements seem to be especially applicable to the compounds we have investigated.

### Studies with Labeled Drugs

Our investigations of the penetration of labeled barbiturates (phenobarbital and thiopental) into the central nervous system and of their accumulation there clearly demonstrate that the prevalent concept of uniform entry and distribution of barbiturates is no longer tenable if one examines drug entry as a function of time after injection and maturity of the animal, with due regard for the anatomical subdivisions of brain (*35, 37*). Sampling of such areas as cerebral hemispheres, diencephalon, brain stem, and cerebellum, without regard for their anatomical subdivision, obscures the differences which become apparent when their substructures are considered separately. By using autoradiography and radioassay techniques which delineate these subdivisions, we found a distinctly nonuniform distribution of phenobarbital, gray matter having been penetrated more rapidly than white (Fig. 9)—a finding which indicates that penetration by phenobarbital, like penetration by urea, is retarded by white matter in the adult cat. An inverse relationship exists in the kitten brain (Fig. 5*C*), where the primordial white areas are more readily penetrated. Presumably this is due to the incomplete formation of the myelin barrier and, perhaps, to the higher content of extracellular water in white matter in the immature brain. As the animal develops and myelination proceeds, the relative ease of penetration of white matter and gray reverses.

It is important to note that no metabolites of phenobarbital were found in the brain, and that while only one intravenous injection of the labeled drug was administered, a nearly constant level was maintained in the circulating plasma. Ultrafiltrates of plasma containing phenobarbital show that this drug is present in the cerebrospinal fluid in the same concentrations as in an ultrafiltrate of plasma. Phenobarbital is found in cerebral cortex and cerebral white matter at levels which indicate a degree of binding quantitatively similar to that existing in plasma, the total levels in cortex being somewhat above plasma levels after 3 hours (see Fig. 9). Although the level of phenobarbital in gray matter was comparable to that in plasma throughout the period of study, cerebral white matter and other myelinated structures, such as the medullary pyramids, did not achieve plasma levels for from 3 to 6 hours. It is evident that the rate of penetration is unrelated to vascularity, since the

highly vascular colliculi and geniculates contained less of the drug than would be expected if vascularity were a controlling factor. The eventual distribution at later time periods was nearly uniform.

Phenobarbital, a barbiturate with slow onset of action but of long duration, contrasts directly with thiopental (Pentothal), which is widely used in anesthesiology because it rapidly produces sleep of short duration. This remarkably early onset of action has been explained on the basis of thiopental's lipoid solubility and consequent rapid penetration into all areas of the brain. The short duration of action has been ascribed to early removal of the drug from the brain into the fat depots of the body (*38*). That fat constitutes the primary depot for removing thiopental from the circulation has been questioned by Goldstein and Aranow, who have demonstrated that total body water, muscle, and other binding sites play the more dominant role (*39*).

Examination, by the techniques of autoradiography and radioassay, of the penetration of thiopental into the brain of a cat reveals an interesting pattern of entry and accumulation not previously noted (*37*). Thiopental is unique among the drugs we have studied in that its distribution is suggestive of the known pattern of vascularity in cortex, geniculates, colliculi, and white matter at 1 and 5 minutes after injection (Fig. 10). We have found, as did Goldstein and Aranow (*39*), an early and high concentration of thiopental in the brain. However, by considering this organ in more anatomical detail, we have demonstrated the nonuniformity of the brain with regard to thiopental penetration and have found that the levels in the cerebral cortex at these early times after injection exceed the levels in plasma by a factor of 2, while a surprisingly low concentration was found in the lipoid-rich white matter. Equilibrium between gray matter, white matter, and plasma is not reached for approximately 30 minutes.

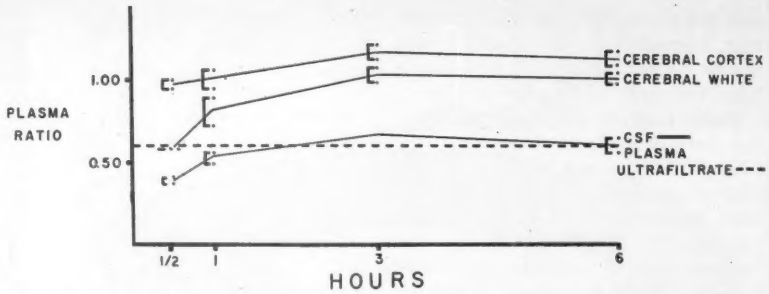



Fig. 9. Levels of $C^{14}$-labeled phenobarbital in cerebral cortex, cerebral white matter, and cerebrospinal fluid as compared with levels in total and unbound plasma. Values are expressed as ratios relative to values for plasma. It may be noted that levels in the cerebrospinal fluid and in the plasma ultrafiltrate are quantitatively comparable, while the total amounts in cortex and in white matter are comparable to the total level in plasma. Equilibration is more slowly attained in white matter than in cortex. [From N. S. Domek, C. F. Barlow, L. J. Roth, *J. Pharmacol. Exptl. Therap.* **130**, 285 (1960)]

As with phenobarbital, the amount of thiopental in the cerebrospinal fluid is comparable to the amount in an ultrafiltrate of plasma. The finding of rapid accumulation or binding of an unusual amount of thiopental in gray matter at 1 minute after injection is in sharp contrast to our findings for phenobarbital. At 30 minutes after injection these distinctions are no longer apparent. The ultrashort action of thiopental (that is, early onset and early recovery) may not be due exclusively to its rapid depletion from brain but may also be related to a rapid fall from unusually high early levels in such gray matter structures as cortex, geniculate bodies, and colliculi. Assay of whole-brain homogenates have obscured these findings, which are clearly demonstrated by autoradiography and regional radioassay. We have detected only unchanged thiopental in brain at 1 and 5 minutes after injection; however, thiopental metabolites may appear in brain at later times.

Acetazolamide (Diamox), a drug designed to produce diuresis by inhibition of the enzymatic conversion of carbon dioxide and water into carbonic acid in the kidney, has also been found to be useful in the treatment of epilepsy. How this drug functions in suppressing epileptic seizures is not known at present, although inhibition of carbonic anhydrase activity in the brain with increase in localized concentrations of carbon dioxide has been suggested. Elucidation of this problem has been hampered by lack of sensitive analytical procedures and further complicated by the fact that this drug is found in brain parenchyma in microgram quantities. Attempts to assay the brain for acetazolamide have been limited to determinations on extracts and homogenates of whole brain—a procedure which does not permit analysis of significant relationships between enzyme and drug in discrete anatomical structures. We found $S^{35}$-labeled acetazolamide to be a convenient tool in our studies, since acetazolamide is not metabolized by the body (*40*). Autoradiography and radioassay reveal a surprising pattern of entry into the brain (*41*). Acetazolamide was found to enter by two distinct routes—the cerebrospinal fluid and the capillary circulation (Fig. 11). A high concentration develops first in the cerebrospinal fluid, with the ventricular walls acting as the site from which the drug diffuses into paraventricular areas. At 4 hours after injection this pattern is further developed. The areas of greatest concentration are still those in close proximity to the cerebrospinal fluid, and considerably more diffusion into periventricular and periaqueductal tis-

Table 1. Influence of carbon dioxide on penetration of test substances. Concentration in brain is expressed as a fraction of levels in plasma. The values are based on radioassay data from M. Goldberg, C. F. Barlow, and L. J. Roth (*34*). Note the disproportionate increase in penetration of white matter by salicylic acid under conditions of hypercapnia. *Gray*, cerebral cortex; *white*, cerebral white matter.

| Area | Concentration in brain | | Relative penetration* |
|---|---|---|---|
| | Hypercapnic acidosis | Hypocapnic alkalosis | |
| | *Urea (1 hr)* | | |
| Gray | 0.40 | 0.16 | 2.50 |
| White | 0.12 | 0.05 | 2.40 |
| | *Phenobarbital (½ hr)* | | |
| Gray | 1.20 | 0.72 | 1.67 |
| White | 1.08 | 0.40 | 2.70 |
| | *Salicylic acid (1 hr)* | | |
| Gray | 0.44 | 0.11 | 4.00 |
| White | 0.38 | 0.04 | 9.50 |

* Relative penetration: brain fraction under conditions of hypercapnia to brain fraction under conditions of hypocapnia.

sues has by this time taken place. However, a second pattern becomes evident as the deeper structures are entered from the capillary circulation.

Eight hours after injection, when the level of the circulating drug has fallen, diffusion from the cerebrospinal fluid is no longer apparent. However, three distinct areas of the brain have retained the drug in relatively high concentration—caudate nucleus, hypothalamus, and hippocampus. Although the hypothalamus and thalamus are similarly exposed to the high concentration of acetazolamide in the cerebrospinal fluid, the hypothalamus retains the drug in high concentration at 8 hours, whereas the thalamus does not. Whatever the significance of the double mode of access in the case of acetazolamide, the regional differences in penetration and retention are more conspicuous with this drug than with any other we have studied. The development of high concentrations in discrete and widely separated structural units not only serves to emphasize in compelling fashion the relevance of cerebral architecture in neuropharmacology, but also strongly suggests some sort of localized and active biochemical binding.

The behavior of $C^{14}$-labeled diphenylhydantoin (Dilantin) is illustrative of an unusually high degree of tissue binding (*42*). This drug has been found to concentrate in the brain at levels that are two to three times the level in the circulating plasma and that persist for 24 hours after a single pharmacologic dose. If one compares levels in the brain with the non-bound, diffusible drug level in plasma, one finds that the brain levels exceed the plasma level by a factor of 10.

We have discussed the manner in which certain drugs, urea, and sulfate have been found to enter the brains of physiologically normal animals. We have noted that diversity is the rule, and that anatomic loci, structure, maturity, and vascularity play unpredictable roles that differ with the substance under investigation. It appears certain that heterogeneity will become increasingly evident as additional drugs are tested. Many more compounds possessing diverse physical and chemical properties will require investigation before valid general rules can be laid down. The role of infection and of the species, state of health, and nutritional, pathological, and physiological state of the animal also bear investigation.

Waddell and Butler (*32*) studied the effect of acidosis and alkalosis on the rate of urinary excretion of phenobarbital and noted that respiratory acidosis increased the concentration of phenobarbital in the total brain. Metabolic acidosis was shown by Gray *et al.* (*43*) to shorten the time required for acetazolamide to reach maximum anticonvulsant activity.

Considering these results, we undertook an investigation of the regional penetration characteristics of phenobarbital and acetazolamide under conditions of respiratory acidosis and alkalosis (*34*). We also included salicylic acid and urea for comparative purposes, since salicylic acid ($pK_a$ 3.0) is a stronger acid than phenobarbital or acetazolamide, while urea is a nonlipoid-soluble neutral solute. Under conditions of hypercapnia (plasma *p*H 6.81) and hypocapnia (plasma *p*H 7.86), marked alterations were found in the penetration of all brain areas by these compounds; penetration increased with hypercapnia and decreased with hypocapnia (Table 1). Furthermore, each of the three ionizable drugs showed proportionately higher concentrations in white matter than in gray under conditions of hypercapnic acidosis. This may be related to suppression of ionization, with presentation to lipoid membranes of a higher concentration of the nonionized, fat-soluble form of the test compound, white matter being particularly sensitive because of the multiplicity of myelin lamellae. Conversely, we find that white matter is poorly penetrated under conditions of hypocapnic alkalosis. The greatest effect is evident with salicylic acid, whose degree of ionization is most strongly affected by variations from normal physiological *p*H. These data are qualitatively compatible with a fourfold increase in the number of un-ionized salicylate molecules calculated for this acidotic state as com-

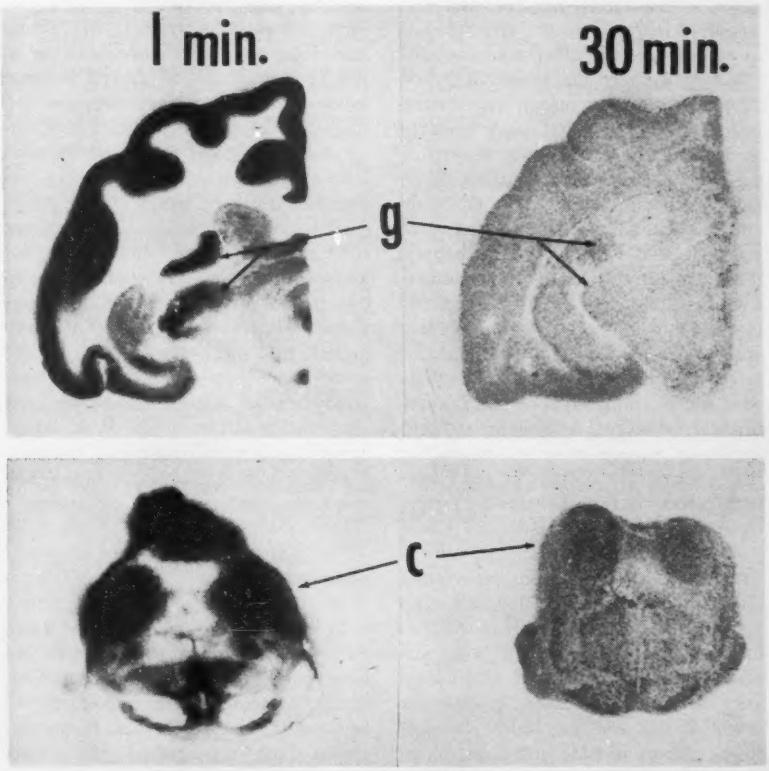



Fig. 10. Autoradiograms recorded after injection of $C^{14}$-labeled thiopental. Animals were sacrificed 1 minute and 30 minutes, respectively, after injection. At 1 minute after injection there is high radiodensity of cortex, geniculate bodies (*g*), and inferior colliculi (*c*), indicating high concentrations of the drug. The pattern is reminiscent of that of blood flow (Fig. 2). At 30 minutes after injection all areas are of almost equal radiodensity.

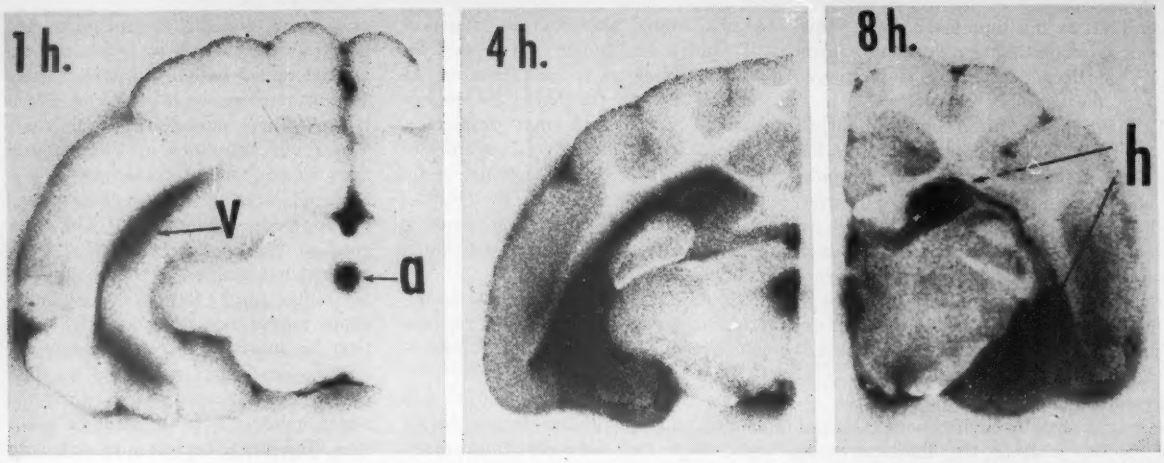



Fig. 11. Autoradiograms recorded at 1, 4, and 8 hours, respectively, after injection of $S^{35}$-labeled acetazolamide. At 1 hour after injection there is high radiodensity of the cerebrospinal-fluid pathways, especially prominent in the lateral ventricle (*v*) and the aqueduct (*a*). However, the line of demarcation between cerebrospinal fluid and brain is not sharply defined, as it is after injection of sulfate (Fig. 4), and a diffusion front is apparent. The autoradiogram recorded 4 hours after injection shows extension of penetration of the drug from the ventricle and aqueduct into adjacent areas of the brain. However, an anatomical pattern distinguishing the cortex from the underlying white matter has appeared, suggesting the more usual blood-to-brain entry pattern. At 8 hours after injection the major point of interest is the heavy radiodensity confined to the hippocampus (*h*).

pared to the normal number, and with a tenfold increase for the acidotic state as compared to the alkalotic state (*34*).

Comparison of the effects of hypercapnia and hypocapnia on the penetration of phenobarbital and salicylic acid, on the one hand, and of urea, on the other, reveals an important difference. Although hypercapnia facilitates and hypocapnia hinders the entry of urea, according to the general pattern, the entry is nonselective, and concentrations in all areas are proportionately increased with acidosis or decreased with alkalosis. This lack of difference in the penetration pattern occurs only with the nonelectrolyte urea. Changes in penetration of urea with administration of carbon dioxide demonstrate that a significant portion of the effects with carbon dioxide are due to factors other than ionic dissociation.

No direct correlation can be demonstrated to exist between penetration and vascularity or blood flow, although it is well known that blood flow is increased by hypercapnia and decreased by hypocapnia. If blood flow were a dominant factor, gray-matter areas should be markedly affected, since carbon dioxide increases blood flow in gray matter more than in white (*44*). Blood flow as a lesser role is shown by our finding that cats, on inhalation of carbon dioxide (5 percent), failed to demonstrate significant variations in brain concentrations of phenobarbital as compared to normal animals, although Kety (*45*) has found that inhalation of carbon dioxide at this level produces a marked increase in blood flow. The highly vascular colliculi and geniculate bodies also failed to demonstrate an increased penetration of drugs even at the highest carbon dioxide levels used.

The exact mechanism of the change induced by carbon dioxide is not known, but as we have indicated, carbon dioxide has a specific and perhaps unique effect on the entry of compounds into the brain—that is, on the blood-brain barrier—above and beyond its effect on dissociation. Further study of a larger series of divergent compounds, with analysis of the contribution of such factors as blood flow and tissue binding, will be necessary.

## Summary

In our studies on the entry of drugs into the central nervous system we have found the technique of autoradiography combined with radioassay to be a valuable research tool. It has disclosed such unsuspected phenomena as the dual routes of entry into the brain of acetazolamide. Although many factors controlling drug entry remain to be studied, we propose certain general conclusions.

1) The anatomical boundaries of brain are clearly reflected by the penetration and accumulation of all compounds we have studied—a finding that confirms the original proposition that whole-brain homogenates are inadequate for the study of drug and brain relationships.

2) Circulation, expressed as regional blood flow or volume of capillary blood, was seldom decisive in influencing entry or accumulation of exogenous substances in the brain. To date, the only compounds demonstrated to be circulation-dependent are trifluoroiodomethane and thiopental. Both are extremely fat-soluble. Tissue binding appears to be an additional factor in the case of thiopental.

3) Penetration is retarded by myelin. All substances we have studied have shown a relatively slower rate of entry into this tissue. In immature brain, before myelinization has taken place, the primordial white matter is readily penetrated. We have suggested that entry into mature white matter is retarded by the lamellated membranes of the myelin sheath, which should be regarded, therefore, as a component of the blood-brain barrier. The small interstitial space indicated by the limited entry of sulfate ion is an additional hindrance to dispersal of exogenous substances into brain parenchyma. The blood-brain barrier is a complex anatomical, physiological, and biochemical phenomenon, and no unitary hy-

pothesis is adequate to embrace all the observed events.

4) Accumulation of a drug in the brain implies some form of binding or interaction between drug and tissue. Findings on injection of phenobarbital, thiopental, or diphenylhydantoin illustrate such an accumulation. These binding interactions may be nonspecific, as is probable in the case of drugs bound to plasma protein. However, a more fundamental significance is suggested when a drug is found to bind, react with, or accumulate in, a specific anatomical structure of the brain. We have made reference to this possibility in connection with the localization of isonicotinic acid hydrazide or its metabolites in the hippocampus (*46*), and we have also reported the striking accumulation of acetazolamide in hippocampus, caudate nucleus, and hypothalamus. Although the binding process is poorly understood, further investigation of these phenomena should lead to a clearer understanding of regional variations in brain chemistry. While one should not assume that the demonstration of a focal concentration of a drug implies site of action, correlation between pharmacological action, electrophysiological events, biochemical changes, and temporal and regional drug concentrations may indeed exist (*47*).

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12. Mongrel cats were injected intravenously with a single dose, in amounts adequate for autoradiography but not exceeding accepted therapeutic levels. Administration of urea in trace doses produced no measurable increase in the total amount of circulating urea, and administration of $S^{35}$-labeled sulfate in trace doses produced no observable pharmacological effect. Radioactively labeled phenobarbital, isoniazid, thiopental, diphenylhydantoin, and acetazolamide were synthesized in our laboratories by Leon Clark. Labeled urea, salicylic acid, and $S^{35}$-labeled sodium sulfate were obtained from commercial sources. The radiochemical purity of each was established by standard chemical methods, including chromatography. The animal was sacrificed at selected times after injection; the brain was removed and cut into sections, which were apposed to photographic film, an autoradiographic picture of isotope localization thus being produced. The autoradiographic findings were supported by dissection and radioassay of 16 anatomically defined areas of cat brain, some as small as the medullary pyramids (*41*); the presence or absence of metabolites was determined by standard techniques. Care must be taken in such studies to secure radiochemical purity of the injected material and to analyze for metabolites in order not to misinterpret the meaning of the assay data or the autoradiogram. It should also be pointed out that the autoradiogram is not quantitative under these circumstances. Artifacts may be introduced by differences in self-absorption of tissues [S. Ullberg, *Acta Radiol. Suppl.* **118** (1954)]. White matter, with its high lipoid content, tends to have a somewhat higher self-absorption. Autoradiograms, therefore, must be evaluated in terms of radioassay of dissected structures.
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# Winter Thermal Radiation Studies in Yellowstone Park

## Infrared reveals surface phenomena of hot springs and temperatures of vegetation and Old Faithful geyser.

David M. Gates

An expedition into Yellowstone National Park, 14 through 23 February 1961 (*1*), afforded an unusual opportunity to measure the thermal radiation characteristics of the natural environment. Yellowstone Park offers great extremes in environmental conditions within concentrated areas, a situation which is particularly unusual during winter months. An object or organism on the earth's surface may be subjected to several or all of the following factors affecting the energy exchange between it and its surroundings: direct sunlight, skylight, thermal radiation, heat conduction, heat convection, evaporation and condensation of moisture, and chemical energy from physiological processes. For objects or organisms on or above the surface of the earth, the one factor which is continuously present day or night, winter or summer, is the flux of thermal radiation exchanged by all exposed surfaces. The thermal-radiation component may be the dominant factor during the night or even during the winter day for controlling the temperature of the object or organism. At other times and during other conditions it may represent only a part of the total energy exchange, perhaps being exceeded only by the direct-sunlight component. In areas where there are thermal hot springs, such as those found in Yellowstone Park, the terrestrial heat may dominate the microenvironment of the surface. For objects at the temperature of most natural surfaces—surfaces such as snow, soil, water, and vegetation—the thermal radiation emitted consists entirely of infrared radiation of wavelengths usually more than 5.0 microns, with the peak of the energy distribution centered at wavelengths of about 10 or 12 microns. In order to detect this energy one must use an infrared-sensitive detector such as a thermocouple, bolometer, or photoconductor. There has been such a distinct paucity of environmental measurements at infrared wavelengths that it was decided to carry out a series of such observations in Yellowstone Park on this occasion. In addition, the infrared detection technique afforded the opportunity to determine the temperature of the clouds formed from the geysers and of other geophysical features.

Various types of infrared-radiation instruments have been designed for meteorological purposes. However, most of these are unsuitable for detailed ecological and geophysical measurements of the type performed here. The instrument selected for this work was the Stoll-Hardy (*2*) radiometer with infrared filter. The instrument was originally intended for physiological applications but can be used to measure the surface temperature of various objects or the "radiant" temperature of environments (*3*). The sensitive element consists of two thermistor flakes located at the apex of a polished cone having a 20° field of view. Two more thermistor flakes, located within the radiometer head and shielded from the incident radiation, form the other arms of a Wheatstone bridge and act as temperature compensators. A microammeter is provided, with three scales (0°–10°, 0°–30°, and 0°–100°C), for making readings of temperatures that depart from ambient temperatures.

The thermistor head is normally placed in a cavity in an aluminum block which acts as the reference temperature unit and to which all other temperatures are compared. The instrument is calibrated by means of a Leslie cube of unit emissivity. Several modifications of the instrument were made to facilitate its use in the field. The ambient aluminum block supplied with the instrument was replaced by a much larger aluminum block in order to give greater thermal stability through increased heat capacity. The detector head was embedded in Styrofoam for further insulation in order that thermal gradients from the hand would not disturb the readings. These two modifications proved very satisfactory in the field. In addition, the instrument was provided with a connector to which an auxiliary battery supply could be clipped, the batteries being kept warm by being worn inside the coat of the investigator. The radiometer is relatively simple and easy to use, but, being a direct-current device, requires special care.

The temperature of a surface is obtained from the well-known radiation law

$$E = \epsilon \sigma T^4$$

where $E$ is the energy radiated in calories per square centimeter per minute, $\epsilon$ is the emissivity of the surface, $\sigma$ is the Stefan-Boltzmann constant in calories per square centimeter per minute per degree Kelvin to the fourth power, and $T$ is the surface temperature in degrees Kelvin. For many surfaces such as soil, rock, or snow the emissivity is unity, and for most vegetation it is 0.95 or better (*4*) in the infrared. If the response of the radiometer (the microammeter reading) is plotted against the energy given off by the Leslie-cube black body, a precise straight line results. Therefore, the instrument measures directly the energy received by the conical head, and this can then be converted to temperature if the emissivity of the surface is known. If the emissivity is less than unity but is assumed to be unity, then the temperature obtained is the "radiant" temperature of the surface. By "radiant temperature" is meant the temperature of a black body radiating the same amount of energy as that received by the detector. The "radiant" environmental temperature of the sky is a somewhat fictitious quantity, since it does not represent the actual true temperature of any part of the atmosphere, but is only a means of expressing the amount of energy received from the

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sky or, effectively, the strength of the sky as a "sink" for infrared radiation. The Stoll-Hardy radiometer has a distinct advantage over other radiation instruments for field use in that its receiving area is small enough and its field of view is sufficiently narrow that it can pick up detailed features of the thermal environment, particularly when it is used close to the emitting surfaces.

### Surface Temperature of Hot Springs

The "radiant" temperature of the surface of some hot-spring pools was investigated. The radiometer "head" was held as close to the surface as possible, usually about 3 millimeters away, and a reading was taken immediately. It was necessary to hold the head close to the surface in order that the moisture in the air would not seriously affect the response through absorption and reradiation. The radiation emitted by the surface of the water originates within the uppermost 20 to 30 microns of the liquid. This can be shown by computation from the absorption coefficients for liquid water given by Dorsey (*5*) for the wavelength region 6.0 to 18.0 microns. The reflectivity of liquid water is 1.5 percent at 8 microns, and hence the emissivity is 98.5 percent. This correction must be applied to the instrument reading in order to obtain the true surface temperature of the water.

When exploring the surface temperature of the hot springs with the radiometer we noticed at certain places that large temperaure differences may exist within a very short horizontal displacement. At first this was thought to be an error, but it was soon discovered that it was a fundamental property of a very interesting phenomenon involving the surface layer.

Most of the hot-spring pools had a thin film on the surface which extended out a distance from the edge determined by the convection currents within the pool and the action of wind stress on the surface. These films were seen to be very thin and were judged to be monomolecular, in view of the interference fringes they displayed. In the case of the Blue Star spring, this film covered the water in the bay or "thumb," to be seen at lower left in Fig. 1, and the approximate point at which the edge of the film crossed the bay is indicated by the arrow. The film also occurred in other parts of the pool, particularly in some of the other bays.


Fig. 1. Blue Star hot spring, where infrared measurements of the surface temperature were made. The diameter of the spring is approximately 15 feet. (×) Point of inflow of hot water; (arrow) the edge between the monomolecular surface film and the free water surface.

The source of hot water flowing into the pool at a constant rate was at the bottom directly beneath the point marked × in Fig. 1. The hot water flowed up and outward toward the edge. Most of the edge of the pool consisted of a thin shelf of rock which was undercut to a distance of about two feet. The water appeared to be circulating to some distance underneath this ledge. The forced convection within the pool was rather strong, and the temperature throughout the pool at a depth of about 30 centimeters, as well as under the surface film in the bay, was 83.8°C. The temperature at a depth of 5 centimeters under the surface film, as measured with a mercury thermometer, was 83.4°C, and at the same depth just beyond the film the tempera-

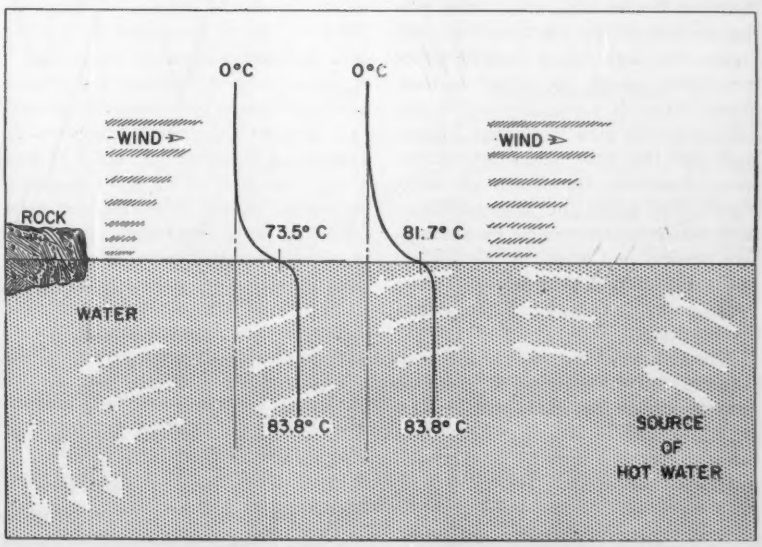


Fig. 2. Schematic drawing illustrating the temperature profile at the water surface and at the water-film surface of the Blue Star hot spring.

ture was 83.5°C. A few millimeters beneath the surface, at a depth just sufficient for immersing the thermometer bulb, the temperature was 82.0°C beneath the film and 82.4°C under the free water surface. The radiometer, when held within 3 millimeters of the surface, indicated a surface temperature of 81.7°C for the free water surface and of 73.5°C where the monomolecular film covered the surface.

This measurement was repeated several times, and the distinction in surface temperature was clearly defined. The results are illustrated in Fig. 2. As the surface film meandered into the bay or farther out, according to the strength of the wind, the surface-temperature boundary shifted with the film. Measurements on other days gave surface temperatures of 79.8° and 70.5°C, 78.2° and 72.0°C, and 80.2° and 69.5°C, respectively, for the free water surface and the monomolecular film. The temperature gradient was measured across the surface-film boundary on another bay at the opposite edge of the pool. The temperatures here were found to be 82.2° and 68.0°C and 76.1° and 69.0°C, respectively, for the free water surface and the monomolecular film. Across this film edge a horizontal difference in temperature as great as 14°C was observed.

It is conjectured that these striking temperature gradients are caused by the differential flow of heat to the surface by internal convection. The surface loses heat through radiation and evaporation. The monomolecular film defines a region where the surface is less disturbed by the wind, due to the protection offered by the rim of rock around the edge, which projects about two inches above the water surface. Warm water is constantly fed to the surface of the pool by forced convection, and this flow mixes the surface layer; however, the stream of warm water slides under the monomolecular film, which is maintained by the surface tension, and leaves at the surface, under the film, a thin layer of water which cools by radiation. These effects are illustrated in Fig. 2.

Another possible cause of the temperature difference may be that the monomolecular film changes the emissivity of the surface. This hypothesis was tested in the laboratory by placing various films, such as oils and turpentine, on a water surface and measuring the surface temperature before and after. No distinction could be detected. One would not expect a difference, on basic

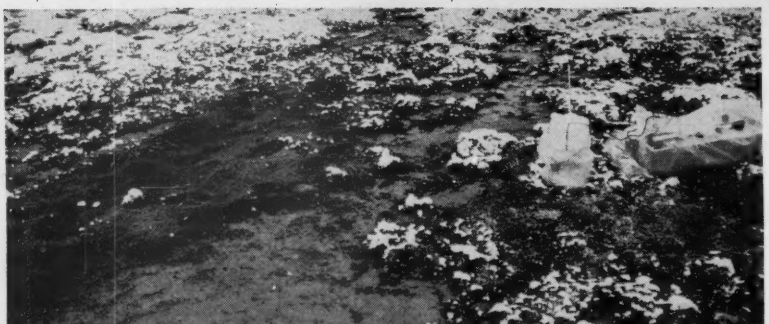

Fig. 3. View of the vegetated thermal area studied, showing the bare soil, the moss, and the grass. The infrared radiometer is at upper right.

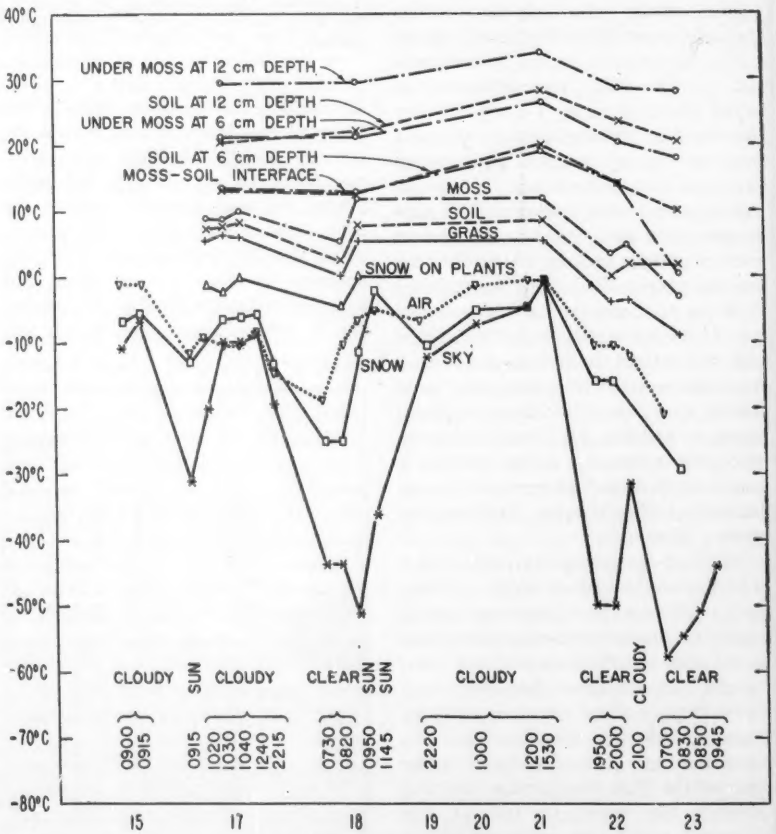


Fig. 4. The surface temperatures of the vegetation, soil, and snow in Yellowstone Park and the "radiant" temperature of the sky during part of February. The temperatures beneath the bare soil and beneath the moss-covered soil are also shown.

principles, but nevertheless the hypothesis required testing. Since the phenomenon seemed to be related to the convection stresses on the surface, we wondered if the monomolecular film might have changed the evaporation rate significantly. This effect was not considered to be important. However, a reduced evaporation rate at the monomolecular film surface would tend to increase the surface temperature rather than decrease it, as observed. A reasonable explanation is the transfer of warm water to the surface by internal forced convection beyond the film boundary and a lack of transport of water immediately beneath the film. Ewing and McAlister (*6*) have also reported an interesting surface-layer characteristic occurring on the ocean, detected by means of an infrared radiometer.

## Thermal Environment of Vegetation

Two thermal areas were selected for a detailed investigation of the radiative characteristics of the surface features. The particular area reported upon here is shown in Fig. 3 and consists of an exposed soil surface, an area of moss (*Rhacomitrium canescens* Brid.), and an adjacent area of grass (*Panicum thermale* Bolander). The surface temperatures of these features were measured on several occasions with the radiometer. In addition, the surface temperature of the snow, where the snow was a foot or more deep, was measured. The radiometer was turned to the zenith in order to determine the "radiant" temperature of the sky. A mercury thermometer was used for measuring the temperature in the soil beneath the moss and beneath the exposed soil surface at several depths.

The results of these measurements are shown in Fig. 4 (it was not possible to make all the measurements every day because of other activities). It is clear that the supply of heat in the ground maintained the surface features at a reasonably constant temperature, but that the changes in temperature which did occur essentially reflected the cooling power of the sky. Part of the time the snow was nearly in radiation balance with the sky, as on 15, 19, 20, and 21 February, when there was a heavy stratus-cloud cover. Trees or animals in the area would have been receiving approximately 0.408 calorie of radiant energy per square centimeter per minute from the snow and sky at −5°C, a value which is nearly half the average energy received from the sun on a summer day. The effect of clouds is clearly seen on 22 February, when the sky temperature changed from −50° to −31.5°C (with a corresponding downward flux of radiation of 0.195 to 0.267 calorie per square centimeter per minute). The surface temperatures of the plants, soil, and snow responded to this increased warmth from the sky. The coldest recorded "radiant" temperature for the sky was −58°C, representing a downward flux of 0.169 calorie per square centimeter per minute. The moss surface was at about −3°C and emitted an upward flux of radiation equal to 0.420 calorie per square centimeter per minute, with a net loss of heat through radiation of 0.251 calorie per square centimeter per minute. Since there was no wind, this figure represents much of the total loss of energy by the moss, the transpiration rate probably being very small. The effect of sunlight warming the plant, snow, and soil surfaces is evident at 0950 on 18 February, even though the sky temperature dropped at this time. It should be emphasized that the energy environment of the Old Faithful area of Yellowstone Park in the winter is predominately a thermal-radiation environment, with the sunlight contributing a relatively small amount of energy to the total energy exchange, and the sun is often masked by heavy cloud cover. Of course, at night the energy environment is completely thermal in character, all the radiation exchange being at infrared wavelengths with a relatively weak convective exchange of energy at the surface, or with none at all.

The other vegetated thermal area studied was measured less frequently. It contained a grass (*Poa annua* Rinnaeus) at a surface temperature between 15° and 16°C on 20 February and between 10° and 11°C on 23 February, and a moss association of *Bryum turbinatum* (Hedwig) Schwager and *Ceratodon purpureus* (Hedwig) Brid. at 19° and 15°C, respectively. The bare rock adjacent to the vegetation was at 19°C on each of the two days.

## Radiant Temperature of Water-Vapor Clouds

Measurements were made, from a distance of about 1 meter, of the "radiant" temperature of the water ejected from Old Faithful geyser during an eruption. A value of 73.5°C was obtained. This would appear to be correct in view of the fact that a great deal of cooler water is expelled with the steam and superheated water from deeper down and that the whole plume of water is pretty well mixed. Although much of the water plume fell back to the ground, the cloud which formed just downwind of the plume had a temperature of about 10°C, and some 20 meters downwind the cloud temperature was −4.5°C, with variations from 4° to −9°C. It is evident that the cooling rate in these clouds is very rapid; however, it is also apparent that a great deal of cooling takes place in the process of cloud formation during the dispersal of water droplets and the mixing with air. The water which fell back on the ground from the plume was at a temperature of 50°C or higher.

Similar measurements were made of the vapor cloud from Castle geyser. The temperature of the vapor cloud just downwind from the water plume was 26°C. At this point the cloud probably contained a great deal of warm water, which was raining out. Less than 15 meters downwind the temperature had fallen to the range −8° to −13°C, approaching the temperature of the ambient air.

The thermal-radiation measurements reported here show the value and feasibility of using an infrared radiometer in the field for measuring surface temperatures of vegetation and terrain, for measuring cloud temperatures, and for studying the surface temperatures of bodies of water. A good infrared radiometer for field work is needed in order that further systematic measurements of this type can be made readily and accurately.

### References and Notes


1. The expedition was sponsored by a National Science Foundation grant to the College of Education (at Albany), State University of New York. I wish to thank Dr. John Marr (director, Institute of Arctic and Alpine Research, University of Colorado) for the loan of the radiometer, which was obtained with a grant from the National Science Foundation. I also wish to thank Dr. William A. Weber (University of Colorado) for identifying the plants; Dr. Claes Rooth (Woods Hole Oceanographic Institution) for his cooperation in making the measurements and for helpful discussions; Dr. Vincent Schaefer, leader and organizer of the expedition, for the opportunity to participate; and the superintendent and personnel of Yellowstone National Park for their excellent cooperation.
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6. G. Ewing and E. D. McAlister, *Science* **131**, 1374 (1960).

# Science in the News

## Disarmament and the Test Ban: Several New Developments Merely Confirm That the Outlook Is Dim

Last week disarmament was in the news a good deal, but none of the news offered any hope for progress in the near future.

The President announced at his press conference that he had asked his Science Advisory Committee to set up a panel to report on the technical side of the test-ban problem: specifically, on how much chance there was of the Russians' carrying out testing without our getting any evidence that it was taking place; how much progress they might be making by conducting the kinds of tests that can be thoroughly concealed; how significant this progress might be in altering the power balance between Russia and the West; and how much we ourselves could expect to gain from a fairly prompt resumption of testing, considering, of course, that the Russians also would restart open testing as soon as we did.

At the same time the Soviet-American discussions aimed at working out the format for general disarmament negotiations continued, although there were good indications that no progress was being made.

Finally, Kennedy carried out a Democratic campaign pledge by sending to Congress draft legislation setting up a major agency devoted to disarmament and related problems.

### Scientific Panel

The announcement of the creation of a scientific panel to report on the test ban must be regarded as primarily a public gesture. The Administration would have been grievously negligent if a panel for just this purpose were not already in existence, continually evaluating whatever new information is coming in affecting the calculation of the risks involved in continuing the current unpoliced moratorium; in particular, a detailed review of this sort certainly was made sometime between the turn of the year and late March to provide the basis for the Administration's policy commitments made when the Geneva talks were resumed on 21 March. Politically, the situation has changed drastically since then: the Russians, as demonstrated, for example, by their insistence on a veto over inspections, have obviously lost interest in reaching an agreement; but technically there has been no hint that the situation has changed significantly, and therefore there is no reason to believe that the report of the new panel will be significantly different from the report that must have been made earlier in the year.

### Neutron Bomb

There has been a good deal of talk lately, of course, about the neutron bomb, but this represents not a new technical factor in the calculation of risks, but a talking point for those who favor a fairly prompt resumption of testing. (Except for those who have been against the test-ban talks all along, such as Senator Dodd, no one seems to be very specific about just how promptly testing should be resumed.)

Although the term *neutron bomb* was not used, and the specific characteristics of the weapon were only vaguely described, an article in *Fortune* a year ago, giving the case for resumption of testing, was apparently based largely on the neutron bomb. The same is true of an article in *Foreign Affairs* of the same period. Both articles stressed the possibilities of a hydrogen (fusion) weapon which would not require a uranium (fission) device to trigger the reaction. The recent flurry of leaks about the neutron bomb have described this weapon in these same terms. The weapon would be triggered by a chemical reaction. The distinguishing feature of this pure-fusion weapon (other types may be theoretically possible, but they have not been publicly discussed) is that it would be comparatively cheap, and compact, and that it would produce comparatively little blast effect. Instead, it would produce an intense flux of high-speed neutrons, capable of destroying all life in the target area, while producing little damage to nonorganic matter. But the target area involved would be small compared with that of "conventional" hydrogen weapons. It would apparently be a tactical battlefield weapon, not a city-destroying strategic weapon. There is disagreement among the scientists involved over the specific characteristics that could be built into the weapon—that is, over how large the effective target area might be and over the speed with which the weapon might be developed.

Most of the news leaks that have produced the recent stories about the weapon have come from Congressional supporters of test resumption: that is, from men who do not have the technical backgrounds to inspire unquestioned confidence in their evaluation of the possibilities of the weapon. Apparently the weapon is about 5 years off, in any case, and no case has been made that a decision to devote a major effort to developing the weapon would be restricted by a continuation of the unpoliced test-ban for, say, another year. Thus supporters of a resumption of testing have seized on the neutron bomb as a dramatic talking point.

But all the talk offers little guidance for the general public in trying to understand the precise basis for whatever decision will be made, a situation which seems unavoidable since the technical arguments are highly sophisticated, and since a good deal of the most essential information on weapon development must necessarily be kept secret. That the Congressional leaks on the neutron bomb do not add up to a case for the fairly prompt resumption of testing does not mean, of course, that such a case cannot be made and that the case will not prove convincing to the Administration.

### Political Questions

On the nontechnical side, the great question that troubles the decision-makers, of course, is in evaluating the harm that will be done if testing is resumed. One view is that if this country resumes testing underground, the Russians will probably resume testing in the atmosphere, and since the American tests would produce no fallout and

the Russian tests would, we would come off better than the Russians. But the world-wide concern over fallout is based not only on calculations of the damage it might cause, which after all is fairly small, but in large part on the revulsion against the development of more horrible nuclear weapons, of which the fallout danger is a by-product. To the extent this is true it does not follow that the world reaction against a possible Soviet resumption of fallout-producing tests would be greater than the reaction against the United States for being the first to resume testing at all, even though the U.S. tests produce no fallout. But no matter how awkward a resumption of testing may be, it remains true, as Administration officials have privately emphasized, that the decision cannot be avoided if it becomes clear that the risks of continuing the voluntary ban while the Russians may be secretly testing simply cannot be accepted.

It is in this connection that the public announcement of the organization of the scientific panel is significant, and it is a safe assumption that the review will be followed by a public report by the panel evaluating the risks of continuing the unpoliced moratorium indefinitely: in other words, the organization of the scientific panel, like the issuance of the White Paper (*Science*, 23 June) last month must be viewed primarily as a move intended to promote general understanding of the reasons for American policies in preparation for a possible resumption of testing, although the White Paper, ostensibly, was a diplomatic note to the Russians and the scientific panel is being set up, ostensibly, to produce an evaluation for the Administration. This does not necessarily mean that a decision to resume testing has yet been taken; it simply reflects the fact everyone now recognizes that there is no likelihood that the Russians are going to agree to a policed test ban in the near future, and therefore that the United States has no choice but to prepare the ground for a resumption of testing if that should prove necessary. Even if testing is not resumed, such steps as the issuing of the White Paper and the convening of the scientific panel would still be extremely useful in making clear to the world why, in our view, the Russians are clearly to blame for the collapse of hopes for reaching a formal agreement.

On the Soviet-American talks aimed at setting up the framework for the general disarmament negotiation which had been scheduled to begin 31 July, both sides promised to keep the exchanges entirely private. Although John J. McCloy, the American representative, refused, for this reason, to discuss this topic with reporters, no one who had talked with him could avoid the impression that very little progress was being made. The first phase of the negotiations ended last week. McCloy arranged for Valerian Zorin, the Soviet negotiator, to pay a call on the President, and it was announced that the negotiations would be broken off for 2 weeks, to resume in Moscow on 17 July.

### Disarmament Agency

The Administration, nevertheless, followed through on its campaign commitment to organize a much-expanded Disarmament Agency. A high Administration official said that the outlook for disarmament is not very bright at the moment but "it's just as important to patch the roof when it's raining as when the sun is shining."

The draft legislation was a long way from the elaborate proposal for a Peace Agency put forth last year by the Democratic Science Advisory Committee. That agency would have pretty much taken over all research related to the world's economic and social problems, as well as its more obvious work on disarmament. The new agency, though, will still have broad research responsibilities, going beyond a narrow definition of disarmament, and, in addition, major operating functions: specifically, carrying on actual negotiations and running the control organization if and when a control agreement is signed.

The new agency will be authorized to sponsor research not only on problems directly involving disarmament and arms control, but in such matters as economic impact of disarmament and the problem of gradually developing a system of international law to provide for peaceful settlement of disputes.

A good deal of this could have been set up simply by making vigorous use of the present Disarmament Agency, which was organized last fall on the basis of a Presidential executive order. But the Administration chose to ask Congress to provide formal legislation, in part to emphasize the importance it attaches to the agency, in part to ease the way for getting appropriations for the agency through Congress.—H.M.

## Salk, Sabin, and the AMA

The American Medical Association has endorsed the mass use of the Sabin oral vaccine against polio, stating that the Salk vaccine, the only one thus far licensed for use here, cannot eradicate polio in the United States. The AMA implied that the oral vaccine, still undergoing tests for safety and potency, should be given, when available, to everyone, even those who have received the full Salk series of three injections and booster.

Jonas Salk protested the implication that the oral vaccine should be given to everyone, including those who have received the Salk series, and termed the AMA endorsement "questionable and of doubtful practicality."

The AMA approval of the Sabin vaccine is the first ever given by the organization to an unlicensed product still being tested. The licensing by the Public Health Service has been delayed by uncertainties about (i) the interaction of the live poliovirus with other viruses in the intestinal tract; (ii) the possible effect of the virus on the central nervous system; and (iii) the dosage schedule for maximum effect. In addition, the PHS requires that five consecutive lots of the virus vaccines, all free of extraneous viruses or other matter, must be produced to assure continuous safety of all lots. The vaccine is produced in monkey tissue which not infrequently demonstrates the presence of other viruses, but manufacturers expect to be able to satisfy this requirement by fall.

The spread of polio in the United States has been markedly reduced by the use of the Salk vaccine. But the method of administration by injection, requiring trained personnel, as well as the time involved in getting the number of shots necessary to build up immunity, has had some limiting effect on the number of people benefiting from it. However, a significant advantage of the Salk vaccine is that it does not reintroduce live poliovirus into the population.

The oral or live-virus vaccine such as the Sabin product has been used with success in the Soviet Union, Great Britain, and in South America. The oral vaccine has been given by teaspoon in a cherry-flavored syrup. Ease in administration has meant wider and faster distribution than can be provided for Salk vaccine. The oral vac-

cine has another advantage in that it is more effective in epidemics. The type of poliovirus that may be involved in an epidemic situation can be isolated and then administered quickly and easily in the oral vaccine to those endangered. This protection cannot be afforded by the Salk vaccine. Neither product, however, is effective if administered to a person who already has been infected by poliovirus.

## Space Pictures

Four photo records of the passage of cosmic rays in space, taken aboard Air Force Discoverer satellites and Atlas rockets, have been recovered, yielding data on the radiation exposure of space vehicles and on the effect such exposure may have on future travelers. The films were part of a series of rocket and satellite experiments planned by the Geophysics Research Directorate of the Air Force Cambridge Research Laboratories to try to find some clues to the source of cosmic rays and how they get their tremendous energies.

Nuclear emulsions much thicker than ordinary photographic emulsions and stacked to provide a three-dimensional pattern were used to trace the path of the rays and measure their flux. The special emulsion stops cosmic rays entering it at angles before they pass completely through, thus capturing a complete record in the form of tracks (see cut).

The first pictures were taken from an Atlas nose cone recovered in July 1959. Emulsions were carried to an altitude of 700 miles, entering the lower Van Allen belt of trapped radiation that encircles the earth. Another Atlas nose cone, recovered in October 1960, also went into the Van Allen region and also carried emulsion packages inside the vehicle near a cage containing three mice that provided data necessary to the design of shielding for astronauts. Cosmic ray tracks on emulsions carried on board Discoverers XVII and XVIII, recovered in November and December 1960, still are being studied. Those from Discoverer XVIII are providing data on cosmic radiation entering the atmosphere over the arctic and antarctic regions.

These photographic records provide detailed analyses of single events; but for over-all pictures of cosmic-ray behavior, instrumentation that does not need to be recovered is carried into space, and the data are telemetered back. Geiger counters and proton spectrometers of the solid-state, scintillation, and Cerenkov types are some of the devices flown.

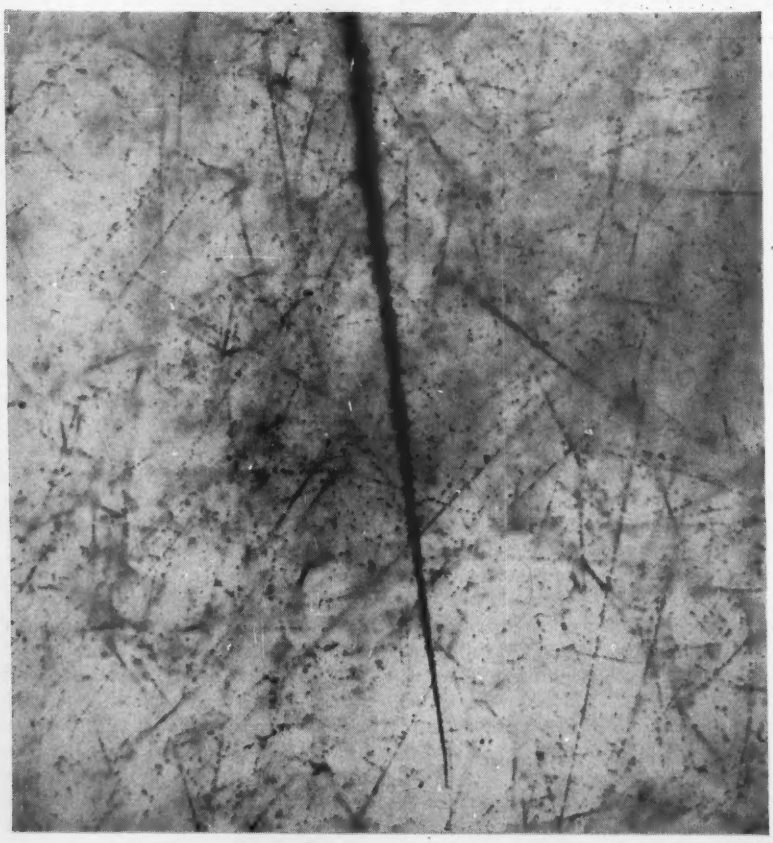
Neutron experiments are being conducted to provide data on the formation of the lower Van Allen belt. It is believed that this trapped radiation consists of protons produced by the decay of cosmic-ray produced albedo neutrons. Blue Scout rockets and satellites to be launched this year will carry boron trifluoride detectors to measure neutron density at various altitudes.

* * *

Daylight pictures of planets, rockets, and missiles, previously unattainable, may now be transmitted to indoor screens, for continuous viewing, by the Facet-Eye camera, developed at the Air Force Missile Development Center, Holloman Air Force Base, N.M. This camera has taken clear daylight pictures of Venus and Jupiter that previously could be taken only at night. Astronomers have expressed interest in the system, according to an Air Force spokesman, although it was designed primarily to make possible a 24-hour viewing of rockets, missiles, and satellites in space. An array of 19 long-barreled telescopes, each focused on the same point in the sky, is used, and the resulting images are then superimposed on one another. The magnification is as great as it would be if one large telescope were used, but the amount of stray light is greatly reduced, and this makes it possible to obtain clear images even in the daytime.

* * *

A missile-tracking ship, the *American Mariner*, carrying more than $30 million worth of radar, infrared, and optical devices, will take up station in the Atlantic Ocean to study launchings from Cape Canaveral. The 90 technicians aboard will concentrate largely on getting records of missiles returning from the upper atmosphere in order to learn more about re-entry behavior. The unarmed vessel is under the Army's operational control.



A typical photomicrograph of tracks obtained during the time Discoverer XVIII's re-entry capsule was in orbit. [Cambridge Research Laboratories, U.S. Air Force]

### Water Pollution Bill

Both the Senate and House have passed bills that will double, to $100 million annually, federal grants to states and local communities for control of water pollution. A Senate-House conference this week was working out the minor differences between the bills, but the result was certain to be a measure costing somewhat more than the bill passed last year and vetoed by President Eisenhower, who said that the problem is "a uniquely local blight" which should be dealt with by state and local action.

The bill passed the House by 198 votes, with nearly half the Republicans joining 90 percent of the Democrats to pile up the 308-to-110 margin. The Senate version passed on a voice vote with little debate. The opposition did not ask for a roll call. As is common on such issues, local governments generally supported federal intervention on the grounds that on these predominantly urban problems the cities simply cannot get the help they need from the rural-dominated state legislatures.

### Research in Materials

The Defense Department, through its Advanced Projects Research Agency (ARPA), has awarded $13.4 million in contracts to universities for basic research in materials, divided among Brown, Harvard, MIT, Chicago, and Stanford. The awards are the latest in a series reflecting a decision made last year at the White House level to strengthen the basic research needed to provide the specialized materials needed by the newer technologies. The atomic plane project, for example, floundered largely because of the inability to develop materials capable of withstanding the high temperatures and high intensity radiation to which the engine components would be exposed, and similar problems come up in connection with developing materials for space vehicles and new weapon systems.

### Small Nuclear Generators

A 4½-pound atomic power unit is generating electricity in the Transit IV-A navigation satellite that was part of the three-satellite "economy package" recently launched by a single 50-ton Thor-Able rocket. Transit IV-A is the first of four operational prototypes of the Navy's satellite navigation system that will beam signals to airplanes, ships, and submarines on weather and location to aid navigation.

The small nuclear generator is supplying power to two of the four radio transmitters in the satellite. The generator contains a small amount of plutonium-238, a radioactive element with a 90-year half-life, capable of generating heat up to 1000°F. The heat is converted by very small thermoelectric rods into electrical energy. The output is 2.5 watts, and the estimated lifetime of the unit is 7 years. Approximately 7000 pounds of ordinary batteries and solar cells would be required to power the transmitters for the same period of time. The success of the unit overcomes a major problem resulting from the breakdown of conventional batteries in satellites.

The unit is one of a series of SNAP (System for Nuclear Auxiliary Power) devices under development by the Atomic Energy Commission to supply energy in space and on earth. The AEC has announced success in developing the first atomic-powered weather station to be installed in the arctic ice north of the Canadian border. The station will derive its power from a generator filled with strontium-90. The generator will power the unmanned weather station on the same heat-to-electrical energy conversion principle as that used in the Transit unit; its output is 5 watts. The station will be able to transmit data every 3 hours for two or more years without refueling.

### News Briefs

A pilot plant to remove strontium-90 from milk is being tested by the government at the Agriculture Department's Research Center at Beltsville, Md. The process would be valuable in case of nuclear attack. The Atomic Energy Commission and the Department of Health, Education, and Welfare are cooperating in this research.

* * *

There were three new appointments to the President's Science Advisory Committee last week: Edwin R. Gilliland, professor of chemical engineering at Massachusetts Institute of Technology; Franklin A. Long, professor of chemistry at Cornell University; and Colin M. MacLeod, of the New York Medical Center.

## Announcements

The **Board of Microbiology** of the American Institute of Microbiology is accepting applications for certification in the fields of public health and medical laboratory bacteriology; public health and medical laboratory virology; public health and medical laboratory mycology; public health and medical laboratory immunology; and in the broader area of public health and medical laboratory microbiology. (American Board of Microbiology, 232 Burrill Hall, University of Illinois, Urbana)

The proceedings of a conference on the results of Commander Shepard's suborbital **space flight** have been published by the National Aeronautics and Space Administration in cooperation with the National Institutes of Health and the National Academy of Sciences. (Superintendent of Documents, U.S. Government Printing Office, Washington 25. Order No. 0-597504. $0.50)

An International Society of **Stereology** (the science of three-dimensional interpretation of flat images) has been formed for the exchange of ideas concerning applicable research methods in microanatomy, cytology, ultrastructure studies, metallurgy, geology, astronomy, and cosmology. Inquiries are invited concerning membership, or the activities of the society. (Hans Elias, Chicago Medical School, 710 S. Wolcott Ave., Chicago 12)

**Weather Modification**, *Second Annual Report, 1960*, describes projects sponsored by the National Science Foundation within this research area, as well as the work of other federal agencies and of state, local, and private groups. The foundation's weather modification program, administered through grants and contracts, expended $1.4 million during fiscal year 1960, an increase of $250,000 over the previous year. "The greatest deficiency in the field of weather modification," the report states, "is skilled manpower. However, for the first time, the United States has launched a sustained and concentrated attack on the problem and . . . has created new research opportunities . . . to attract . . . young scientists to work on the problem in our graduate school laboratories." (Superintendent of Documents, U.S. Government Printing Office, Washington 25. $0.15)

## Meeting Notes

A **World Health Conference**, on such international problems as nutrition, environmental health, mental health, communicable and infectious diseases, nursing care, and health education in underdeveloped countries, will be held at the University of California, Los Angeles, 6–7 October. (Department of Continuing Education in Medical and Health Sciences, UCLA Medical Center, Los Angeles 24)

A conference on the **cervix**, sponsored by the New York Academy of Sciences, will be held 7–9 December at the Barbizon-Plaza Hotel, New York.

An international symposium on **tissue transplantation** will be held in Santiago and Valparaiso, Chile, 30 August to 2 September. The symposium, sponsored by the University of Chile and the learned societies of Santiago and Valparaiso, will cover the genetical basis, immunological problems, present status, and prospective applications of tissue transplantation. (Alberto P. Cristoffanini, Organizing Committee, Symposium on Tissue Transplantation, Máximo Humbser 567, Santiago, Chile)

## Grants, Fellowships, and Awards

Applications are being accepted for basic research fellowships in the field of **central nervous system disorders**. Deadline: *1 November*. (National Neurological Research Foundation, 3255 N St., NW, Washington 7, D.C.)

A $1000 award is being offered for the best treatise concerning **parapsychology** and its relation to other scientific disciplines. A bibliography is available to applicants at nominal cost. Deadline: *15 December*. (Administrative Secretary, Parapsychology Foundation, Inc., 29 W. 57th St., New York 19)

Mathematicians who plan to attend the **International Congress of Mathematicians** to be held in Stockholm, 15–22 August 1962, may apply for travel grants through the National Academy of Sciences–National Research Council. Deadline: *1 November*. (Division of Mathematics, NAS–NRC, 2101 Constitution Ave., Washington 25, D.C.)

## Scientists in the News

**George Nevitt**, regional dental consultant with the U.S. Department of Health, Education, and Welfare, has been named director of the department's new National Dental Health Center established on the grounds of the Public Health Service Hospital, San Francisco. The center will provide facilities for applied research in the prevention and control of dental diseases, and for training dental public health workers in the application of research findings.

**Raymund L. Zwemer**, former assistant science adviser of the Department of State, has been appointed associate editor of the *American Journal of Physiology* and the *Journal of Applied Physiology*, publications of the American Physiological Society.

**George Schmidt**, associate professor of physics at Stevens Institute of Technology, has been named head of the institute's new theoretical plasma research program, established with a $17,000 contract awarded by the Atomic Energy Commission.

Recent staff appointments at the Biologics Testing Laboratory, Worcester, Massachusetts:

**Harris Rosenkrantz**, research associate at the Worcester Foundation for Experimental Biology, has become director of biochemistry.

**Zarah Hadidian**, liaison officer with the Office of Naval Research in London, has become director of pharmacology and toxicology. Hadidian has been on leave of his duties as assistant professor of pharmacology at Tufts University School of Medicine since 1958.

**Edward W. Strong**, professor of philosophy at the University of California, has been named chancellor of the Berkeley campus, effective 1 July.

**G. W. H. Schepers**, pathologist for E. I. du Pont de Nemours and Company, Wilmington, Del., has received the 1961 Industrial Medicine Association merit in authorship award for his contributions to industrial medicine.

**Ernest C. Faust**, emeritus professor of parasitology at Tulane University School of Medicine, has received the Colombian decoration of the Order of San Carlos for his service under the Tulane-ICA-Colombia program in medical education. Faust served as resident consultant for the seven medical schools in Colombia.

**Ernest Knobil**, Richard Beatty Mellon professor of physiology and chairman of the department at the University of Pittsburgh, has received the 1961 Ciba award of the Endocrine Society.

**Moses S. Strock**, assistant professor of oral surgery at Tufts University School of Dental Medicine, has been appointed associate clinical professor of dental medicine at Harvard School of Dental Medicine.

Recently appointed professors at the Rockefeller Institute:

**George E. Uhlenbeck**, formerly Henry Smith Carhart university professor of physics at the University of Michigan;

**Theodore H. Berlin**, former professor of physics at Johns Hopkins University;

**Mark Kac**, former professor of mathematics at Cornell University.

**Clinton C. Powell**, deputy chief of the National Institutes of Health's division of research grants, has been appointed assistant director of the National Institute of Allergy and Infectious Diseases.

**Max K. Horwitt**, associate professor of biological chemistry at the University of Illinois, has received the 1961 Osborne and Mendel award of the American Institute of Nutrition.

## Recent Deaths

**K. A. Allen**, 36; chemical technologist at Oak Ridge National Laboratory; 14 June.

**Walter L. Bierring**, 92; retired Iowa State health director and former president of the American Medical Association; 24 June.

**Herbert G. Dorsey**, 85; physicist and inventor in oceanography, radio, and telephones; chief of the research section, U.S. Coast and Geodetic Survey, from 1926 until his retirement in 1948; 24 June.

**Albert Deutsch**, 55; journalist specializing in psychiatry; 18 June.

**Francis Pottinger**, 91; authority on chest diseases, and past president of the American College of Physicians; 10 June.

# Earth and Beyond

## The International Geophysical Year in retrospect: Was it a "turning point in history"?

Sydney Chapman

"Looking back upon the IGY, there seems little doubt that it marked a major turning point in history." Thus writes Walter Sullivan, the gifted and learned chief science writer for the New York *Times*, in the last chapter of his fascinating book about the International Geophysical Year—**Assault on the Unknown** (McGraw-Hill, New York, 1961. 461 pp. $7.95). At the close of the last IGY Assembly in Moscow (1958) I gave a more modest estimate: ". . . a time will come when our great enterprise, the IGY, will be viewed as an important but primitive landmark in the history of man's exploration of the cosmos." But it cannot be doubted that the IGY also had significant political results. It made valuable contacts possible between the scientists of the East and the West, contacts that were previously handicapped by inhibitions on both sides. And it led to the drafting of the Antarctic Treaty that aims to exclude military action from Antarctica.

Some research scientists look down their noses at science journalists. Certainly garbled accounts of what has been gathered in reading or at interviews are often presented by some science writers to their readers. Sullivan's book is a fine vindication of the value of good scientific reporting, both to the public he mainly aims to serve and to science. From the early days of IGY planning and development Sullivan enabled readers of the New York *Times* to follow its progress, whereas the Manchester *Guardian* could refer in its columns to "the mumbo-jumbo of the IGY."

In his reports Sullivan helped to inform an important section of the U.S. public on the aims and significance of the IGY. He traveled to many sites of IGY research, near and remote, and made well-used contacts with large numbers of scientists engaged in its varied programs. Thus, and by his reading, he gained an exceptionally wide and balanced knowledge of its vast scope and, later, of its results so far obtained. His new book, the fruit of years of such effort, marks an important stage in the presentation to the public of the IGY harvest to date. It deserves, and will certainly gain, wide and appreciative acceptance from a large circle of readers. Like everything human, it is not perfect. But to draw attention here to the very few and minor errors noted would be to give them disproportionate emphasis. A reviewer may better privately help the author to eliminate them from later editions.

Several books as well as multitudes of articles have already been written about the IGY. Many more will be written, and there is need for them. Sullivan in his preface indicates that "more space has been devoted to the United States effort than to that of any other nation"—as is very natural. "Nevertheless the author has sought to bring out the international character of the IGY. . . ." In this Sullivan's approach is fair and impartial. But the IGY was so extensive in scope that even as ample a book as *Assault on the Unknown* must deal but scantily with many aspects of interest. Ten years hence, and subsequently, scientific historians should have many other and later accounts, by authors of different backgrounds and knowledge, from many lands, on which to base more definitive studies.

The author, former president of the Special Committee for the International Geophysical Year (CSAGI) set up by the International Council of Scientific Unions to coordinate the IGY, is now associated with the Geophysical Institute, College, Alaska; the High Altitude Observatory, Boulder, Colo.; and the Institute of Science and Technology, University of Michigan, Ann Arbor. He reviews here three books: *Assault on the Unknown; Man and Space;* and *A Hole in the Bottom of the Sea.*

### Journalistic Quandary

One of the major chapters of the book is devoted to that wonderful, global, U.S. experiment known as "Argus"—the series of high-level, nuclear bomb explosions suggested by Nicholas Christofilos. This project was outside the U.S.-IGY program, in one sense, but IGY colleagues in other lands might with some justice charge inadequate disclosure of information in connection with it. This event, besides its intense scientific interest, illustrates the quandaries in which journalists are placed, when they obtain information that its originators wish to keep secret. Officials may regard the acquisition of such information as receipt of stolen property, or as larceny by finding. But officials keep secret many things that should be revealed. Debate on such points has lately been revived in another context, and may never lead to agreed conclusions. In another chapter Sullivan summarizes much unpublished correspondence from the central IGY Bureau, without indicating how it was obtained.

The 12 main branches of the IGY scientific program are discussed in turn, naturally with different degrees of competence and completeness. Much analysis of IGY data is still in progress, but major attention is given to the two most outstanding branches of the program—those concerned with Antarctica and the artificial earth satellites. Probably the greatest discoveries made during the IGY concerning the earth and space beyond relate to the oceans, Antarctica, and the Van Allen belts.

### IGY as a Political Example

The harmonious development and execution of the IGY enterprise set a pattern that might serve as an example to be emulated in more difficult, political fields. Two of the very few discords that marred the perfection of IGY harmony are discussed at some length—the entry and exit of the Peking Academia Sinica as a participant and the American discontents at the 1958 Moscow Assembly. In both cases it seems to me that political hands were thrust unwisely and with only harmful effect into our scientific affairs.

So many people and nations gave their best service to the IGY that mention of them in due degree is impossible in such a book. References to

particular contributions must depend much on the author's partly fortuitous contacts. Among the national programs those of the U.S.A. and the U.S.S.R. were pre-eminent, but Japan's effort was so great (having regard to its resources) that it deserves special comment. As to the contributions of individuals, the same may be said of Nicolet and Laclavère; their work, though not unmentioned, was outstanding in amount and range, and it is continuing.

It was difficult, even for those most closely connected with the IGY plan, to get as broad a picture of the whole enterprise as is now portrayed in *Assault on the Unknown*. Scientists and nonscientists alike will welcome this interesting presentation of the scope and achievements (to date) of the IGY.

### Assault on Space

In **Man and Space** (Harper, New York, 1961. 184 pp. $4.95), another eminent science writer, Ralph E. Lapp, describes the background history, development, and results of the space researches undertaken during and since the IGY—thus overlapping *Assault on the Unknown*, though with more detail in many respects. But as the subtitle, "The next decade," indicates, a main purpose of his book is to discuss future objectives in space research, and the present plans to achieve them. Though now a writer and lecturer, Lapp has held important posts in government scientific institutions, and at the end of World War II he was assistant director of Argonne National Laboratory. His experience as an active scientist and administrator adds weight to his words, which are clear, illuminating, and outspoken. They include individual characterizations such as "personable" (page 41), "Washington-wise" (page 42), "imaginative and resourceful" (page 46), and so on. Opinions may differ as to whether occasional pungent remarks hit the mark or go too far beyond it—for example when he comments on the plus and the minus, to the National Aeronautics and Space Administration, of its endowment with the National Advisory Committee on Aeronautics as "encumbering" NASA with the "barnacles and deadwood of an old-line government bureau" or when he refers (page 27) to the National Academy of Sciences as "a rather somnolent organization of elderly scientists," unmindful of the Academy's highly successful management of the United States' great national IGY program. Indeed there is a strong contrast between the attitudes adopted toward the IGY in *Assault on the Unknown* and in *Man and Space*, which mentions it only twice, incidentally, on pages 28 and 51.

### America's Space Effort

As Sullivan also indicated, with reference to the satellites, *Man and Space* points out (page 28) that "The Soviets were not nearly so close-mouthed as they are often believed to be." The fact was that in the United States and elsewhere "No one paid much attention" —or even knew of the advance Soviet information. Chapter 4 ends with the following interesting lines: "If the Soviets are the first to send astronauts to the moon, the first to man a huge earth satellite, the first to land on the moon, then the world will appraise the American space effort as second best. For myself, I find that the 10-year U.S. space program is adequate scientifically, but I do not believe it to be really competitive with the Russians in the real space race. The penalty for starting so poorly in the contest is that we must now make up for the lost years; this inevitably means an accelerated program and a doubling or tripling of the space budget."

Together with much technical discussion of the hardware and instruments of space research, *Man and Space* includes brief but well informed descriptions of its scientific problems and objectives. Lapp outlines the nature of the moon and planets and considers the likelihood or otherwise of life existing on them. Within its relatively short compass the book covers its subject in a clear and enlightening way, which will be appreciated by many readers among both the general and scientific public. They will be helped by the glossary with which the book concludes.

### Project for Future Research

**A Hole in the Bottom of the Sea** (Doubleday, New York, 1961. 352 pp. $3.95) is Willard Bascom's story of the Mohole project. Here he deals with a more limited field of future scientific exploration. He describes the background and plans for the official U.S. effort to explore the earth's crust and mantle. This effort dates from 1958 when the U.S. National Academy of Sciences assumed sponsorship of the deep-hole project. Bascom is now the "director of the Mohole project" for what is called the AMSOC committee in the Academy's Division of Earth Sciences. AMSOC stands for the American Miscellaneous Society, an informal group of scientists connected, in some cases tenuously, with the Office of Naval Research. Its activities are described in a manner at times facetious, and this facetiousness also occurs elsewhere in the book. The name for the project, Mohole, is in the same vein, "honoring" Mohorovičić (whose portrait is given), the Croatian scientist who first indicated the presence of a major discontinuity of earth structure about 55 kilometers deep. The discontinuity is now regarded as the division between the crust and mantle of the earth.

The book opens fancifully with an imagined scene on board ship when the first sample of the mantle is drawn up from a hole drilled right through the crust. It then describes Charles Darwin's proposal, made in 1881, for experimental drilling of coral atolls to 500 or 600 feet and shows how this idea was extended as seismic researches gradually revealed many main features of the inner structure of the earth. Succeeding chapters are entitled: "Science fiction and pseudo science inside the earth"; "Evidence in the rocks"; "Exploring the crust with gravity"; "Probing with earthquakes and explosions"; "The examination of the oceans"; "Magnetism, heat, and pressure"; "Evidence in the skies"; "Objectives and sites"; "Modern oil-well drilling"; "The oil rig goes to sea"; "Experimental holes in deep water"; "On to the Moho"; "The future."

The author writes mostly in a plain matter-of-fact way, easily understood by general readers. He covers a wide field, partly beyond his main experience as an engineer specially associated with oceanography. He is enthusiastic for the project, whose success is made more promising by the exploratory drillings off California, under the auspices of his committee, since his book went to press.

More than *Man and Space*, and much more than *Assault on the Unknown*, this book is "domestic" for the U.S. public. Many scientists of other nations, some of them contemporary,

are mentioned in the background chapters. But little stress is laid on the desirability of international cooperation in the study of the earth's mantle by drilling. The IGY is mentioned only once, incidentally, and only brief reference is made to the active interest in the project shown by the International Union of Geodesy and Geophysics (IUGG). It is related (page 50) that when IUGG considered the project at Toronto in 1957 ("prodded by AMSOC members and by Dr. Tom Gaskell, a British geophysicist"), a resolution supporting it was adopted, and that "a Soviet scientist" arose and said: "We already have the equipment to drill such a hole, we are now looking for the place." By the following September, Bascom states, the Soviet Academy of Sciences was rumored to have appointed its equivalent of a deep-drilling committee. Regrettably (doubtless because of the date on which the book went finally to press) it is not mentioned that at the Helsinki meeting of IUGG (July 1960) the deep hole was a main subject of the presidential address by V. V. Beloussov. He was a member of the central IGY bureau and is now head of the geophysical committee appointed by the U.S.S.R. to organize their part of the effort to complete, continue, and extend the work of the IGY.

The IUGG appointed an international organizing committee, presided over by Beloussov, to further the study of the mantle by deep drilling and in other ways. The mantle should be probed at more than one point, and international pooling of experience and results is obviously desirable.

**Future International Cooperation**

The wonderful response by so many nations to the scientist-originated proposal for the IGY is encouraging for the future. Governments and academies alike should keep it in mind as a stimulus to further action. Amidst much that is good in the individual and organized efforts of mankind, greed, pettiness, and duplicity show their ugly faces. Perhaps the best counteraction is positive cultivation of the impulse to cooperate and emphasis on the generous aspects of emulation. Scientific projects beneficial to our race as a whole give ample scope for this. Geophysics offers several: besides the deep hole studies there are world weather research and the World Magnetic Survey. This last is a deferred item in the IGY program, and one that needs indefinitely continued, periodic repetition; it should be organized permanently and internationally. Most of all, academies and governments should make an urgent resolute push to exclude military efforts from space exploration, as has been done for Antarctica.

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## Aztec Culture Today

**The Virgin's Children**. Life in an Aztec village today. William Madsen. University of Texas Press, Austin, 1960. xv + 248 pp. Illus. $4.50.

Most educated Americans know something about the prehistoric cultures of the Aztecs and Mayas, but they are surprised to discover that descendants of these Middle American civilizations are still vigorously carrying on many fundamental aspects of their ancient traditions. It is true that the decendants no longer build pyramids, sculpt images of their aboriginal gods, or paint murals. But they speak Nahuatl or Maya as their primary language, grow corn and make tortillas, and maintain many more aspects of their ancient social structures and belief systems than I think anyone would expect in the mid-20th century.

Throughout large areas of central Mexico there are still an enormous number of Nahuatl-speaking communities which have yet to be studied by anthropologists. The Nahuatl peoples living in and around the Valley of Mexico are clearly descendants of the Aztecs whose ancient capital of Tenochtitlan has become modern Mexico City, second largest city in the Western Hemisphere. In 1952 Madsen selected the small village of San Francisco Tecospa (population 800) in the Milpa Alta district just south of Xochimilco for a 16-month field study of contemporary Aztecs.

In this delightfully written book Madsen has two purposes: to provide an ethnographic description of the culture of this Aztec village and to elucidate the cultural processes, especially syncretism, by which this culture came to be a complex combination of the ancient Aztec heritage and the Spanish Catholic traditions of the conquerors. The San Francisco Tecospans now regard themselves as children of the Virgin of Guadalupe, but this Catholic virgin is still called Tonantzin and is obviously closely related to the old Aztec earth goddess of that name.

On the whole the book comes off well, and it is an important contribution to our knowledge of contemporary Aztec ethnography and to our understanding of the processes of cultural change. It also has some weaknesses. If Nahuatl is the primary language in San Francisco Tecospa, one wonders why Madsen did not present Nahuatl terms for all the tools, customs, and concepts that he discusses instead of giving some in Nahuatl and some in Spanish. The reader has no way of determining whether the Spanish terms are actually used by the Tecospans themselves or whether perhaps Madsen presents the Spanish terms simply because he used Spanish rather than Nahuatl as his basic field language. At several points I had the impression that the analysis was not as penetrating as it might have been. Instead of a carefully worked analysis of certain aspects of the social structure and of the structure of the belief system, one finds pages of anecdotal material drawn from Madsen's field journal. While this style of presenting ethnography is vivid and will undoubtedly capture the imagination of the layman, it will not satisfy the professional anthropologist interested in problems of social structure and culture patterns.

The book is beautifully illustrated with photographs taken by Madsen and drawings by a Tecospa boy, both of which add much to the understanding and appreciation of the culture of the community.

EVON Z. VOGT
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## Young Intellectuals

**Gifted Children**. Their psychology and education. Maurice F. Freehill. Macmillan, New York, 1961. 412 pp. $5.50.

*Gifted Children* is a comprehensive book that deals primarily with problems of educating gifted children and secondarily with the psychology of gifted children. How to identify gifted children is the first educational problem discussed. Two basic methods are given for solving the problem: obser-

vation and testing. Administrative devices—including grouping, acceleration, and enrichment—are described, and examples of each are given.

Educators will probably be most interested in the three chapters that describe curriculum and methods for teaching the gifted; programs in mathematics, in language, arts, and social studies, and in science are included. Discussion of vocational guidance and of the role of parents rounds off the educational topics.

Sprinkled throughout the book are chapters dealing with the psychological aspects of giftedness. Freehill differentiates among the terms *genius, talent,* and *giftedness,* although he makes little attempt to define gifted children, except by example. Intelligence is analyzed, and its growth and development are considered. Problems of learning and teaching such as motivation, transfer, evaluation, and structuring are discussed. In the final chapter the author discusses the development of emotions and character. In view of his interest in the psychology of gifted children, it is surprising that Freehill devotes only a few pages to the discussion of underachievement.

The book is a good one for in-service educational courses for teachers as well as for graduate teacher education courses in the education of the gifted.

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## Polymer Chemistry

**Preparative Methods of Polymer Chemistry**. Wayne R. Sorenson and Tod W. Campbell. Interscience, New York, 1961. viii + 337 pp. Illus. $10.50.

*Preparative Methods of Polymer Chemistry* deals with the details of polymerization of a very wide variety of important polymers and gives practical and detailed procedures for the synthesis and for the handling of these polymers. The preparations are the sort that could be accomplished in any well-equipped organic laboratory. In many cases the authors checked out the syntheses.

I feel that this will be a most useful book to a great number of chemists and that it fills a very definite need.

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## Atomic Constants

**The Fundamental Atomic Constants**. J. H. Sanders. Oxford University Press, New York, 1961. 88 pp. Illus. $1.60.

One of the types of information hardest to find in a concise and readable form is recent experiments on fundamental constants in physics. Although many of the handbooks which are published from time to time give the latest values of fundamental physical constants, the values are usually presented in lists or tables; thus, it is impossible to come to any valid conclusion regarding the relative merits of various experimental values. It is, therefore, very good to find a small book devoting its pages exclusively to the problem of measurements of $e$, $h$, $m$, $N$, and $c$.

A teacher lecturing in modern physics always likes to have on hand information about the various ways in which the fundamental constants are measured and about their interrelations. Sanders' book is written in a way that makes the job of the physics teacher very easy and gives him enough background information so that he can present a consistent picture of experimental methods in determining acceptable values for the fundamental constants. In this the author has done a real service: he has discussed the newest methods in considerable detail, compared them with the older methods, and still kept his whole contribution to less than 100 pages. I am sure it would have been much easier to write a much longer treatise, but Sanders has accomplished the difficult job of presenting this material in a clear and brief fashion. It is certainly a book I would recommend not only to the teachers of physics but also to graduate and undergraduate students who need a source of ready reference to the precision of the constants which they must use.

The book is divided essentially into three parts: The early measurements of these constants, considerable detail on measurements of the velocity of light, and finally recent precise measurements and derivations of the best values. This arrangement is well thought out for the useful role which this small book will enjoy.

For the research scientist, the author has produced a very carefully indexed bibliography, so that the details on any particular measurement can be followed through the literature without difficulty. This is an essential part, since the book is a short review and since the detailed methods of treating the experimental data and of making the appropriate corrections have not been included. On the other hand, these details, which are of interest primarily to those trying to arrive at their own conclusions as to the best values can be located easily in the appropriate sources.

This small book is a welcome addition to the trend of producing monographs on specific subjects, designed to reduce the labor in finding one's way through the ever-increasing jungle of periodical literature.

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## Bacterial Genes and Viruses

**Papers on Bacterial Genetics**. Edward A. Adelberg. Little, Brown, Boston, Mass., 1960. xlvi + 400 pp. Illus. Paper, $4.50.

**Papers on Bacterial Viruses**. Gunther S. Stent. Little, Brown, Boston, Mass., 1960. xxx + 365 pp. Illus. Paper, $4.50.

**Milestones in Microbiology**. Translated and edited by Thomas D. Brock. Prentice-Hall, Englewood Cliffs, N.J., 1961. xii + 275 pp. Paper, $3.95.

Joshua Lederberg's compilation entitled *Papers in Microbial Genetics, Bacteria and Bacterial Viruses* (1951) appeared on the eve of great discoveries which materially increased our understanding of the fields covered. Edward Adelberg and Gunther Stent, two University of California scientists, have now selected additional papers and present them in two volumes. Adelberg's collection includes 27 articles; Stent's 25. Each volume begins with an editorial review and a bibliography: bacterial genetics, 177 titles; bacterial viruses, 164. The introductions themselves are valuable orienting, critical, and comprehensive reviews. "No apologies need be offered for a selection which must be largely arbitrary." Originally designed to aid students, the collections will prove of value to investigators and professors. All articles selected are presented in English and all tables, graphs, illustrations, and article bibliographies are included.

Different is the selection of historically important papers included in *Milestones in Microbiology* by Thomas D. Brock (Indiana University). Here,

again, is a paperback prepared for students but valuable to more advanced microbiologists. How many of us have read the 1898 report of Loeffler and Frosch on foot-and-mouth disease? *Milestones* begins with Fracastoro (1546) and ends with Woods (1940) on *p*-aminobenzoic acid and sulfanilamide action. There are six headings: "Spontaneous generation and fermentation" (covering the years 1677–1897, 16 articles); "Germ theory of disease" (1546–1882, 11); "Immunology" (1798–1895, 7); "Virology" (1898–1935, 4); "Chemotherapy" (1897–1940, 5) and "General microbiology" (1875–1924, 12). All selections are in English, but five also appear in an appendix in French. Bibliographies are omitted, and some condensation has been effected—"most nineteenth century workers were verbose."

If professors use these volumes wisely, they will be valuable teaching adjuncts, but scientific literature and history are continually being made. The papers presented should be added to, and inclusions and exclusions should be debated. Last, in view of professional tradition, one can be critical of the presentation of all of these articles in English.

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## Paleocene Flora

**The Lower Tertiary Floras of Southern England**. I. *Palaeocene Floras, London Clay Flora* (supplement). Text and atlas (2 vols.). M. E. J. Chandler. British Museum (Natural History), London, 1961. xi + 354 pp. Atlas, 34 plates. £10.

In 1933 E. M. Reid and M. E. J. Chandler published a 550-page monograph describing some 250 species of fossil fruits and seeds collected from "the stiff brown clay" found chiefly on the shore of the island of Sheppey on the north coast of Kent, southeast England, near the mouth of the Thames. This monograph climaxed a more than 250-year interest in the London Clay fossils, an interest that commenced with the sharks' teeth mentioned in the diary of John Evelyn in 1668.

Reid and Chandler's brilliant contribution unfolded a dramatic story of altered geography and shifting limits of land and sea for northwest Europe and of an evergreen, tropical rain forest, of present Indo-Malayan affinities, thriving in southern England and continuously along the north shore of the warm-current, ancient Tethys Sea that connected, through the Mediterranean, with the Indian Ocean.

Chandler's new monograph is in large part a supplement to the London Clay flora, and it is the first of a comprehensive series that will be devoted to early Tertiary plants of southern England. It considers mainly the "angiosperm fruits and seeds of the Palaeocene floras (pre-London Clay) and . . . those of the London Clay not previously described." Leaves are generally disregarded unless related fruits are known. Wood, pollen, spores, and diatoms are reserved for later papers.

The monograph is based on specimens laboriously collected from fresh and reworked exposures from six principal Paleocene and Lower Eocene horizons in the London and Hampshire basins. The fortuitous conditions which permitted the accumulation and preservation of such an enormous number of fruits and seeds is remarkable. More remarkable is the fact that the 500 species now known are probably only a small proportion of the plants "present in life" in England in the early Tertiary. The feat of recovering so many specimens and species is further impressive since most of the outcrops erode rapidly and many of the remains themselves quickly decompose once exposed.

The main body of the work (286 pages) contains records or detailed systematic descriptions of some 500 species, distributed in more than 140 genera and about 62 families. Nine families and 29 genera are not previously recorded in the London Clay flora. Many of the genera are form genera, or they are extinct. Others are identified as living genera or are considered closely related to living genera. The specimens are described with a thoroughness and competence that characterizes the London Clay monograph, and they are beautifully illustrated in an accompanying atlas in 34 photographic plates and by 54 diagramatic drawings in the text.

The systematic portion is prefaced by a briefer introduction (51 pages). The general scope is indicated by a partial listing of topics: mode of occurrence of fossils and collecting methods, physiographic background and geological records of the Poltavian flora (tropical flora of Indo-Malayan type), conditions of deposition and character of the successive beds, recent work on phytogeographic relations of London Clay flora and climate. A table (pages 8–9) shows correlation of early Tertiary beds of the Hampshire and London basins and relates them to the continental stages of Wrigley and Davis (1937) and Arkell (1947). A map (page 10) shows Eocene physiography of southeast England; the present limit of Eocene rocks; the Eocene limits of fluviatile, estuarine, and marine sediments; and the minimum extent of the Lower Eocene (Ypresian) Sea. Named Paleocene and Eocene species are listed with localities on pages 21 and 24 and 39 to 48.

As a supplement, the present volume is not disappointing in comparison with the London Clay monograph, although it is mainly descriptive. It is to the credit of Reid and Chandler that recent botanical knowledge of the tropical rain forests of the southeast Asian areas and the addition to the fossil flora of several elements, including the Rhizophoraceae (mangroves), has strengthened the similarity between the Indo-Malayan and London Clay flora and mainly confirmed their interpretation of the early Eocene paleoecology of Southern England. Their views concerning the nature of pre-London Clay floras in northwestern Europe are, however, modified. Reid and Chandler believed the antecedent Cretaceous and earlier Tertiary floras of that area to be of a much cooler type than characterized the early Eocene, and "direct migration of the London Clay flora from Indo-Malaya itself along the northern shores of the Tethys was explicitly stated. . . ." As the result of recent paleobotanical work in England and elsewhere, Chandler now thinks that a Poltavian type flora occupied the entire area bordering the Tethys, and recolonized newly exposed land surfaces in northwest Europe following regression of the Upper Cretaceous sea. She shows that the pre-London Clay floras of Britian contained definite tropical forms; some were among the more characteristic or common elements of the London Clay flora.

If other papers in this series are of the caliber of this present volume, they will be worthy additions to paleobotanical literature.

JANE GRAY
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# Exploration of Venus by Radar

## Precision range and velocity data can be obtained with a supersensitive radar receiving system.

W. K. Victor and R. Stevens

*Abstract.* A new tool is available to scientists for exploring the solar system, and modern-day explorers are discovering new worlds by radar. On 10 May 1961 a radar signal was beamed at the planet Venus, and for the first time in history the return echo was detected within a few minutes. A new value for the Astronomical Unit has been determined. The data indicate that Venus rotates slowly and that it is a better radio reflector than the moon.

Radar contact with the planet Venus was established almost daily from 10 March to 10 May 1961 at the Goldstone tracking and communications station of the Jet Propulsion Laboratory, California Institute of Technology (*1*). Hundreds of hours of recorded data about the planet were collected.

The principal result of the experiment was the determination of a new value for the Astronomical Unit. At present our best value is 149,599,000 kilometers, and we believe this number is good to 1 part in $10^5$, or approximately 1500 kilometers. However, further data reduction and analysis will probably reduce the uncertainty in the value to ±150 kilometers by July or August.

In addition, spectral analyses of the reflected signal indicate that Venus rotates at an extremely slow rate, perhaps as slow as once every 225 days, which is the number of Earth days required for Venus to orbit the Sun.

Venus appears to be a much better radio reflector than the Moon. Relative to a polished conducting sphere of equal size, Venus appears to have a reflectivity of 10 to 15 percent at 2388 megacycles per second (Mcy/sec). Similar experiments on the Moon with our continuous-wave bistatic radar produce reflectivity numbers of 2 percent.

The authors are on the staff of the Jet Propulsion Laboratory, California Institute of Technology, Pasadena. Mr. Victor is chief of the Communications Systems Research Section. Mr. Stevens is chief of the Communications Elements Research Section.

### Experimental Conditions

The polarization of the transmitted signal was normally right-hand circular, and the receiving antenna was designed to accept reflected signals that were left-hand circular. When the polarization of the transmitting antenna was reversed, the reflected signal was approximately 12 decibels (db) lower than the signal with normal polarization. Had Venus been a polished conducting sphere, the mismatched polarization would have produced a signal 20 db lower (due to the ellipticity of the transmitting and receiving feeds). Since similar experiments on the Moon produced a signal which was also 12 db lower for the mismatched polarization, this finding probably indicates that the surface roughness of Venus is quite comparable to that of the Moon when the roughness is commensurate with the wavelength of the radio-frequency signal.

For the experiment the Goldstone station was converted from its normal configuration to a high-capability planetary radar. The characteristics of the radar (see Table 1) were as follows: The transmitter had a continuous-wave output of about 13 kilowatts at a frequency of 2388 Mcy/sec. This radio-frequency power was fed to an antenna 85 feet in diameter which concentrated the signal into a conical searchlight beam about 0.35° wide in the direction of the planet. Venus was illuminated to the extent that about 10 watts were intercepted by its surface. Apparently about 9 of the 10 watts were absorbed, and the remaining 1 watt was scattered more or less uniformly in all directions. The 85-ft (diameter) receiving antenna, located about 7 miles from the transmitting antenna and shielded by natural terrain, intercepted the return signal and delivered to the receiver a typical input signal of about $10^{-20}$ watt, or −170 dbm. The capability of the receiver system in a typical configuration (see Fig. 1) was such that the $10^{-20}$-watt signal was about 10 times stronger than the noise; or, in other words, with a typical threshold of −180 dbm the signal-to-noise ratio was 10 db. The total system temperature with the antenna aimed at Venus was typically 60°K, and the bandwidth of the receiver was about 1 cy/sec. The contribution to the system temperature, due to the presence of Venus in the antenna beam, was measured to be approximately 0.5°K.

Four different receiver configurations were utilized, and four different types of data were gathered: (i) received signal level, (ii) power spectrum of the reflected signal, (iii) Venus-Earth velocity, and (iv) Venus-Earth range. The signal level and power spectrum data were gathered with open-loop receiver configuration (see also Fig. 1). The velocity and range data were obtained with closed-loop automatic tracking receivers. The signal-level data were used to establish the radio reflectivity of Venus, the power spectrum to determine the rotation of Venus. The velocity of Venus with respect to Earth was measured by comparing the frequency of the Venus-reflected signal with the transmitted frequency. The accuracy of the velocity measurement is 1 part in $10^5$ without further data

Table 1. Venus radar system parameters.

| Parameter | Value |
|---|---|
| Unmodulated transmitter power (12.6 kw) | + 71 dbm |
| Transmitter antenna gain | 53.8 db |
| Transmitter line loss | 0.3 db |
| $\sigma/4\pi R^2$ at 31 million miles | − 84 db |
| Power intercepted by Venus | + 40.5 dbm |
| $(\lambda/4\pi R)^2$ at 31 million miles | −255 db |
| Receiving antenna gain | 53.5 db |
| Maximum received signal level | −161 dbm |
| Apparent reflection and propagation loss | 9 db |
| Typical received signal level | −170 dbm |
| Receiver threshold ($T$, 60°K; bandwidth, 1 cy/sec) | −181 dbm |
| Typical signal-to-noise ratio | 11 db |

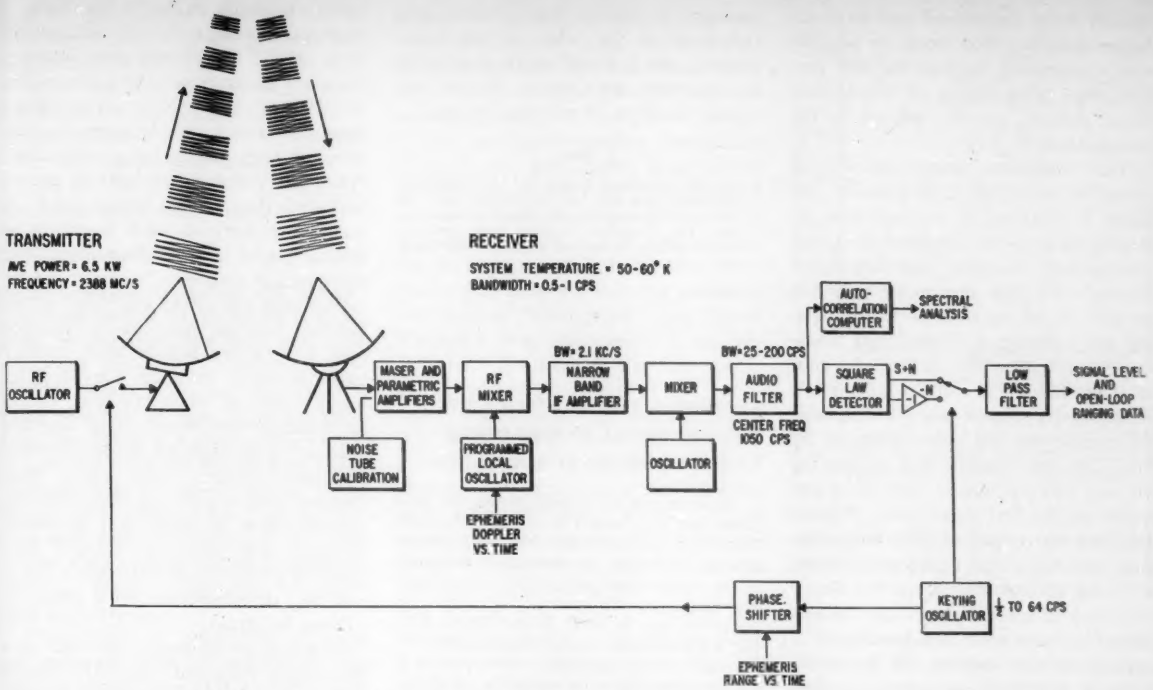


Fig. 1. Venus radar with nonsynchronous open-loop receiver.

smoothing. The width of the closed-loop range gate was 8.2 milliseconds; therefore, we believe that the accuracy of the time-of-flight measurement was about 1 millisecond in a typical round-trip flight time of $3 \times 10^5$ milliseconds. Our new value for the Astronomical Unit was determined from both velocity and range data. Both the radio-frequency signal used for velocity determination and the modulation frequency signal used for range determination were derived from an atomic frequency standard which is believed to be accurate to 1 part in $10^9$ for the duration of the experiment and easily stable to 1 part in $10^{10}$ over the flight time of the signal from Earth to Venus and back.

The rotation rate of Venus may be determined from the Doppler spread (see Fig. 2) if the surface is rough enough to send returns from a considerable area on the surface and if the axis of rotation is known. Because the roughness of Venus with respect to our radio signal appears to be similar to that of the Moon, we assumed for the preliminary analysis that the same scattering law is applicable. The measured frequency spread of the Venus echo was about 5 to 10 cy/sec at the 3-db points and appeared to be quite stable over the 2 months' time for the experiment; therefore it was also assumed that the axis of rotation was not pointing directly at Earth. Based on these apparently reasonable assumptions, Venus appears to rotate very slowly, and this estimate of slow rotation rate is, of course, in agreement with other astronomical observations.

## Effect on Radar Astronomy

The 1961 radar contact with Venus may be expected to have a significant effect on the nation's planetary program, on the new science of radar astronomy, and on observational planetary astronomy in general. For example, the Venus radar experiment will undoubtedly advance the gathering of significant data about Venus by at least 1½ years. This was accomplished by measuring the exact distance to Venus before the launching of the first Venus probe by the United States. Without this information the first spacecraft would have missed Venus by at least 20,000 miles, and another attempt could not have been made for 19 months. One of the objectives of the first Venus spacecraft, of course, was to establish the value of the Astronomical Unit. Fortunately, the Astronomical Unit has

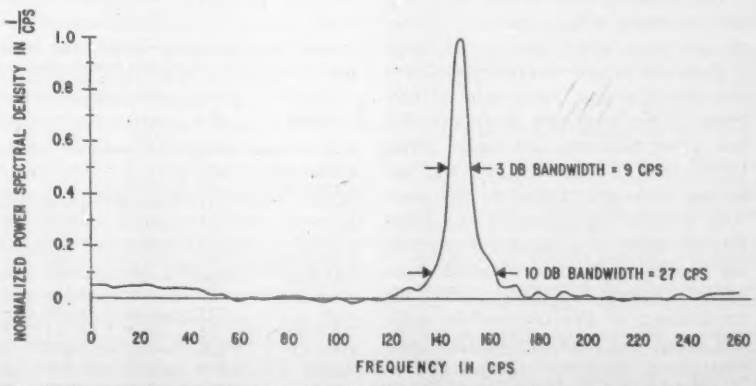


Fig. 2. Venus-reflected signal, 21 April 1961. Spectral analysis, using special autocorrelation computer with nonsynchronous receiver (integration time, 1 hr 23 min).

already been determined and to much higher accuracy than would be possible with a spacecraft, because the very precise angle observations of Venus over many decades can be utilized in the computation.

The Goldstone radar achieved its superior performance principally because it contained a supersensitive receiving system—as opposed to transmitting with extremely high power, for example. For this reason the receiving portion of the radar is presently capable of detecting a 50-milliwatt transmitter located on the surface of Venus at a distance of 30 million miles while radiating its power omnidirectionally. By comparison, the transmitters on the first Explorer satellite had outputs of 10 and 100 milliwatts, and the transmitter on the first lunar probe, Pioneer IV, had an output of 250 milliwatts. This capability will undoubtedly influence the choice of missions for future planetary spacecraft and may be expected to accelerate the landing of a capsule on the surface of Venus to measure temperature, pressure, wind velocity, and other scientific data in preparation for the first manned exploration to the planets.

Until this year the science of radar astronomy had been restricted to gathering and analyzing data principally about the Moon and the Sun. This science has now received new impetus with the gathering of hundreds of hours of data about Venus. The fact that Venus is now within radar range will encourage scientists to search for still more sophisticated techniques to map the surface features of Venus, to determine whether its surface is liquid or solid, and to discover the presence or verify the absence of an ionosphere, a magnetic field, or other phenomena of scientific interest on Venus.

But probably one of the most significant results of this experiment is that we now know how to specify and design a planetary radar observatory which is capable of almost continuous surveillance of our planetary neighbors, Venus, Mars, Mercury, and Jupiter. Prior to this year this information was not known with any degree of certainty. And because the precision range and velocity data of a radar complement the precise angle data obtained from optical devices, we believe that the combination of data obtained by radar and optics will permit the future computation of planetary ephemerides to much greater precision than heretofore believed possible. Such precision will undoubtedly reveal many minor perturbations in the orbits of the major planets, which could make it possible to discover new minor planets and natural satellites of our solar system.

**Note**

1. The Jet Propulsion Laboratory is operated by California Institute of Technology for the National Aeronautics and Space Administration. The Goldstone tracking and communications station is part of NASA's Deep Space Instrumentation Facility.

5 June 1961

## Correlation between Mean Litter Size and Mean Life Span among 12 Inbred Strains of Mice

*Abstract.* In 12 inbred strains of mice there was no general correlation between litter size and parental life span within strains, although a significant between-strain correlation of +0.69 was found between mean life span of the dams and the mean size of their litters. When data for AKR/J mice, which characteristically die early from leukemia, were excluded, the correlation was increased to +0.90 for the remaining 11 strains. These findings indicate that the correlation is of genetic origin—that is, that genes affecting a dam's life span also affect the size of her litters.

Life span and litter size in mice are components of fitness, both affected by genetic constitution and environment. The present study was undertaken as part of a search for correlates of life span. It is an attempt to determine whether the environmental factors in this laboratory which influence litter size also influence parental life span and whether litter size and parental life span are genetically correlated.

Breeding records and life span data for 12 inbred strains of mice were made available to us through the kindness of Elizabeth S. Russell. These animals were bred and maintained in the pedigreed expansion stocks of the Jackson Memorial Laboratory. All strains had been inbred by brother-sister matings for many generations in this laboratory. Under the system used in the pedigreed expansion stocks, complete breeding records for each mating were maintained. When the breeders reached the age of 11 mo, they were retired and in many cases were set aside in groups of two to five to live out their lives. The pairs usually continued to be caged together until one of the pair died. If the survivor was the male, he was recaged with a surviving female from another pair. In some instances surviving females would be caged together, but in no instance were males caged together because of the fighting habits of males of many strains. The cages were checked once a week for dead animals, and the date of death was recorded. In some cases moribund animals were killed to obtain fresh histological material for determination of disease incidence by strain.

Breeding performance and life span data were tabulated for 1717 mated pairs of mice which had had at least five litters. It is known that litter size generally increases with parity, reaches a maximum, and then declines (*1*). If data from all mice had been included, the resulting mean would have been more heavily weighted by the smaller early litters, and mean litter size would have been partially a function of mean reproductive life. Therefore, only data from pairs having five or more litters were included, and the average litter size per dam was calculated from her first five litters. Life span data were computed for the breeding pairs whose litters were used to compute mean litter size. This procedure tended to result in stratification of the sample in favor of good breeders and longer lived animals, since any

Table 1. Within-strain correlations and strain parameters for the variables, litter size ($x$ in mice), dam life span ($y$ in days), and sire life span ($z$ in days).

| Strain | $N$ | Within-strain correlations | | | Strain statistics (means ± standard error) | | |
|---|---|---|---|---|---|---|---|
| | | $r_{xy}$ | $r_{xz}$ | $r_{yz}$ | $\bar{x}$ | $\bar{y}$ | $\bar{z}$ |
| C57BR/cdJ | 135 | −0.15 | −0.17* | +0.24† | 6.34 ± 0.10 | 551.2 ± 10.6 | 483.3 ± 10.7 |
| C57BL/6J | 377 | −0.02 | −0.01 | +0.14† | 5.91 ± 0.06 | 600.4 ± 7.5 | 533.3 ± 0.8 |
| 129/J | 51 | +0.25 | +0.24 | +0.13 | 5.78 ± 0.15 | 543.6 ± 16.0 | 577.8 ± 17.1 |
| RF/J | 31 | +0.27 | −0.18 | +0.34 | 5.48 ± 0.70 | 513.6 ± 62.8 | 578.2 ± 64.4 |
| C57L/J | 82 | +0.06 | −0.23* | +0.25* | 5.39 ± 0.12 | 548.4 ± 13.0 | 538.0 ± 15.6 |
| C3HeB/FeJ | 143 | −0.19* | +0.01 | +0.16 | 5.37 ± 0.09 | 543.6 ± 10.8 | 549.5 ± 10.6 |
| BALB/cJ | 164 | −0.05 | −0.03 | +0.25 | 5.20 ± 0.09 | 506.8 ± 8.8 | 494.4 ± 11.0 |
| AKR/J | 79 | +0.07 | +0.16 | −0.05 | 5.20 ± 0.09 | 319.8 ± 8.6 | 291.1 ± 6.5 |
| A/J | 177 | +0.04 | +0.08 | +0.26‡ | 4.97 ± 0.07 | 441.5 ± 7.5 | 488.0 ± 9.5 |
| DBA/2J | 82 | +0.06 | +0.01 | +0.21 | 4.74 ± 0.10 | 458.6 ± 11.4 | 419.7 ± 11.8 |
| DBA/1J | 226 | +0.02 | +0.03 | +0.11 | 4.42 ± 0.06 | 431.6 ± 5.6 | 453.1 ± 9.7 |
| A/HeJ | 170 | +0.07 | +0.05 | +0.21† | 3.91 ± 0.06 | 395.0 ± 6.5 | 461.2 ± 9.2 |
| Total | 1717 | 0.00 | 0.00 | +0.18‡ | | | |

* $p < .05$ (all two-tail tests). † $p < .01$. ‡ $p < .001$.

Table 2. Between-strain correlations for the variables, litter size ($x$ in mice), dam life span ($y$ in days), and sire life span ($z$ in days).

| $N$ | $r_{\bar{x}\bar{y}}$ | $r_{\bar{x}\bar{z}}$ | $r_{\bar{y}\bar{z}}$ |
|---|---|---|---|
| | *All strains* | | |
| 12 | +0.69* | +0.37 | +0.76† |
| | *All strains except AKR/J* | | |
| 11 | +0.90‡ | +0.58 | +0.67* |

* $p < .05$ (all two-tail tests). † $p < .01$. ‡ $p < .001$.

pairs in which one partner did not survive long enough to produce five litters were rejected. Because early deaths include the majority of deaths from infectious diseases, the net effect was to favor selection of mice dying primarily from degenerative diseases of aged mice. A comparison of our life span data with that tabulated by Russell for the entire group from which these mice are but a sample indicated that our life span values were greater for all strains, but that the order of longevity by strains was not altered.

Coefficients of correlation between the three variables ($x$, mean litter size of dam; $y$, life span of dam; $z$, life span of sire) were calculated both within and between the 12 strains (Tables 1 and 2). Three of the 24 within-strain correlations between litter size and life span of dam or sire ($r_{xy}$ and $r_{xz}$) were significant at the 5-percent level. There was no evidence from a homogeneity test that the within-strain correlations were not drawn from the same population of correlations, so it was proper to calculate total within-strain correlations (*2*). Both the $r_{xy}$ total and the $r_{xz}$ total were zero. (A correlation of +.040 with an $N$ of 1717 would be necessary for significance at the 5-percent level, one-tail test.) Thus, the three significant correlations do not indicate a general within-strain correlation and are probably due to sampling variation. A lack of correlation within strains indicates that for good breeders (i) there is no evidence of an environmental correlation between litter size and parental life span and (ii) if there is any genetic heterogeneity remaining within strains, there is no genetic correlation between these variables. The existence or nonexistence of an environmental correlation between the variables is of course dependent upon the particular environment in which the mice are raised. The mice in these laboratories are raised under uniform conditions in so far as possible. An environmental correlation would be expected between the variables if such factors as food, cleanliness, temperature, and so forth, varied extensively within the animal quarters. Also there is a possibility that a within-strain correlation between these variables may exist for dams who have less than five litters.

The significant positive correlation between dam and sire life spans within strains suggests that cage environmental factors are contributing significantly to the determination of life span. Since the dam and sire were in all cases litter mates, they shared a maternal and cage environment throughout their lives. Therefore, this relationship is not unexpected. No attempt has been made to estimate which aspects of the maternal or cage effects may be most important in producing the correlation.

Between-strain coefficients of correlation between the three variables were also calculated (Table 2). A significant correlation of +0.69 was found between strain mean litter size and strain dam life span. A graphical plot of the data (Fig. 1) reveals that the only strain deviating seriously from a linear relationship between these variables is AKR/J. This deviation is not unexpected because 80 percent of the deaths in this strain are due to leukemia where a virus-inciting agent has been strongly implicated (*3*). Therefore, the primary cause of death may be an environmental agent rather than a constitutional degenerative disease (*4*). When the data for strain AKR/J are excluded from the computation, the between-strain correlation between mean dam life span and mean litter size was +0.90. It is interesting that this correlation exists in spite of the tendency for some strain specific pathologies among aged mice (*5*). There is no reason to suspect that environmental differences between strains is contributing to the correlation; during the duration of their lives the mice had been moved about the laboratory quarters. In addition, at any one time, the strains were dispersed over shelves and in varying degrees in a vertical direction.

There exist some genetic relationships among these strains (*6*), and thus the actual degrees of freedom are not as high as $N - 2$. There are three groups which contain strains that are related as sublines from an inbred line: (i) DBA/1J and DBA/2J, (ii) C57BR/cdJ and C57L/J, and (iii) A/J and A/HeJ. The separations of these sublines occurred many generations ago, and there is much evidence of genetic differences between the strains within the groups. However, if the strains within the groups are lumped in order to approach greater genetic independence between strains, the $r_{\bar{x}\bar{z}}$ becomes +0.94, $N = 8$, $p < .001$; and $r_{\bar{x}\bar{y}}$ becomes +0.69, $N = 8$, and $p < .05$ (AKR/J excluded).

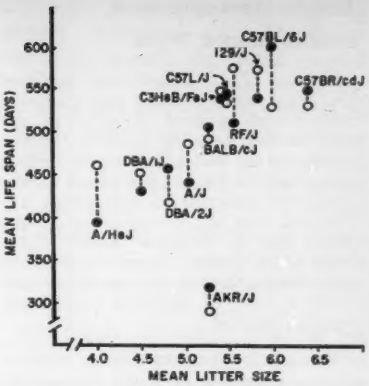


Fig. 1. Litter size and life span for 12 inbred strains of mice. A solid circle represents mean dam life span; a clear circle represents mean sire life span.

The correlation between strain mean litter size and strain sire life span was positive but not significant ($r_{\bar{x}\bar{z}}$ all strains = +0.37, $p \cong 0.20$; $r_{\bar{x}\bar{z}}$ all strains but AKR/J = +0.58, $p \cong 0.05$). These correlations of strain mean litter size and strain sire life span are not significantly different from the correlations of strain mean litter size and strain dam life span (*2*).

The between-strain correlation of sire and dam life spans ($r_{\bar{y}\bar{z}}$) are considerably larger than the within-strain correlation (total $r_{yz}$), indicating that a major part of the correlation is due to a genetic correlation between the variables (*7*).


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4. For the same reason, data on C3H/HeJ were not tabulated since the females are known to carry a mammary tumor inciter which results in early death from mammary tumors. Data for the closely related but agent-free strain, C3HeB/FeJ, are included.
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27 December 1960

## Termite Attractant from Fungus-Infected Wood

*Abstract.* Field observations suggested that subterranean termites might follow a concentration gradient of attractive material to find decaying wood. Laboratory cultures of the brown rot fungus, *Lenzites trabea* Pers. ex. Fr., on pine blocks formed a material attractive to the eastern subterranean termites, *Reticulitermes flavipes* (Kol.) and *R. virginicus* Banks, and a Costa Rican termite, *Nasutitermes columbicus* (Holmgren). Such a potent termite attractant may be useful in termite surveys and control.

The diet of subterranean termites consists primarily of wood infected by fungi. Such fungi may be either beneficial or detrimental to the growth of the insects (*1*). Observations of the eastern subterranean termite, *Reticulitermes flavipes* (Kol.), suggested that a fungus or fungal product might also help the termites locate decaying wood. Shelter tubes built by this termite were found on buildings and trees in Sheboygan, Wis. Such tubes on the bark of living trees invariably led directly to a dead, decaying branch stub. The possibility that the termites followed a concentration gradient of attractive material to find the decaying wood led to laboratory studies on the relationship of termite to fungus.

Eight species of fungi associated with wood decay or termites (*2*) were cultured, and the attractancy of the products to *R. flavipes* was assayed. Culturing was accomplished with soil bottles containing a thin strip of wood called the feeder block. The bottles were inoculated with fungi and then incubated at 80°F at 70 percent relative humidity until the feeder blocks were covered with mycelium (*3*). Autoclaved (15 lbs, 15 min) blocks (¾ by ¾ by 2¾ in.) of western pine sapwood, *Pinus monticola* Dougl., were inserted in the bottles on top of the feeder blocks, and the cultures were incubated an additional 15 or 20 days. Next the test blocks were removed and marked at the upper limit of mycelial growth. Some of the blocks could be demarcated into three regions as follows: (i) a basal region covered by older woolly mycelium, (ii) a mid-region covered by cottony mycelium, and (iii) a top region with no visible mycelium. The mycelium was then brushed off, and each block was cut into sections according to the marked regions.

The blocks (either subsections from fungus-infected wood or control blocks from soil bottles not inoculated with fungi) were placed on moist sand in a large plastic container. Termites (250 of mixed castes excluding macropterous forms) were scattered over the sand in this multiple-choice situation. Within 2 minutes the termites clustered primarily around the basal portion, or woolly mycelium region, of blocks infected with *Lenzites trabea* in each of three replicated containers. Smaller groups of insects gathered around the basal portions of a few of the other blocks infected with other species of fungi. However, the basal portion from blocks infected with *L. trabea* was much more attractive than portions of the other blocks were. After 1 hour the greatest congregation of termites in the three boxes still occurred around the basal portion of the blocks infected with *L. trabea.*

For further studies a more refined bioassay technique for the attractive material was developed. Small paper pads as used in antibiotic assay (12.7 mm in diameter) were placed in a dish 5.3 cm in diameter. The basal portion of the block infected with *L. trabea* was macerated in distilled water to obtain an aqueous extract. A 0.03-ml portion of the extract was placed on one pad, and 0.03 ml of water was placed on another pad in the dish. When 20 termites were introduced they congregated within 30 sec on the pad containing the extract of wood infected with *L. trabea.* This response occurred despite the fact that the termites were in the light and exposed to desiccation. Neither water nor organic solvent extracts of sound wood or of *L. trabea* mycelium grown on malt agar medium elicited any response similar to comparable extracts from the infected wood. Further studies showed that the aqueous extract from 1 g of dry wood could be diluted to 6 liters with distilled water, and 0.03 ml was still adequate for attraction of the termites. Partial purification of the attractive material has been effected. The attractant was extracted from the aqueous material with ether. The ether-soluble materials were then chromatographed on Florisil columns with a benzene-ether elution gradient. The attractant eluted at about a 95:5 benzene-ether mixture. At this stage in the purification, the termites respond to 0.1 $\mu$g of the resulting colorless oil.

The aqueous extract from wood infected with *L. trabea* was also found to be highly attractive to other earth-dwelling termites, such as mixed castes, excluding macropterous forms, of *R. virginicus* Banks, and for nasute and worker forms of a Costa Rican termite, *Nasutitermes columbicus* (Holmgren).

The potential uses of such an attractant in survey, control, and research have been considered in a recent review on the general subject of insect attractants (*4*). Similar uses might be made of this termite attractant from fungus-infected wood (*5*).

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16 March 1961

## Initiation of Flower Buds in Rhododendron after Application of Growth Retardants

*Abstract.* Vegetative terminals of azalea (*Rhododendron* spp.) plants of varying ages initiated flower buds promptly after application of the chemical growth retardants, tributyl-2,4-dichlorobenzylphosphonium chloride (phosfon) and (2-chloroethyl) trimethylammonium chloride (CCC), as soil drenches. This response occurred under environmental conditions which prevented or limited flower bud initiation in untreated plants. Normal flowering followed exposure of the treated plants to dormancy-breaking cool storage.

Application of the growth retardants phosfon (tributyl-2,4-dichlorobenzylphosphonium chloride) and CCC [(2-chloroethyl) trimethylammonium chloride] caused suppression of vegetative growth and prompt initiation of flower buds in azalea, *Rhododendron* spp. These responses did not depend on

minimum age or size of plant, specific photoperiod, or temperature. In the garden azaleas normally initiate flower buds under the high temperatures and relatively long photoperiods of late summer. Bud development continues for several months. Flowering can be accelerated by exposure of the plants to temperatures of 5° to 10° or 12°C for about 4 to 6 wk. Plants grown continuously in the greenhouse initiate flower buds and bloom irregularly throughout the year. Azaleas are reported to be day-neutral (*1*), although long photoperiods promote shoot growth (*2*). Recent work (*3*) suggests that very long photoperiods delay flower initiation in some cultivars of azalea.

Cuttings of *R. obtusum* (Lindl.) Planch., cultivar Coral Bells, were propagated 25 March 1960. The plants were grown in 3-in. pots on natural days in a greenhouse maintained at a minimum night temperature of 15° to 16°C. A terminal flower bud produced on each cutting resulted in physiological pruning and the production of a whorl of new shoots. Later these shoots were pruned by removal of the apical 1 to 2 cm in order to stimulate development of additional vegetative shoots. On 6 October, when the new shoots were 8 to 10 cm long, four lots of plants were treated by adding 79, 197, or 395 mg of CCC or 66 mg of phosfon per plant (all dissolved in 50 ml of water and applied as a soil drench). Half of the plants in each lot were held at a temperature of 12° to 13°C from 9 November until 21 December. To prevent leaf drop during this cool storage the plants were lighted 12 hr daily with incandescent filament bulbs (150 watts) suspended 3 ft over the plants. The appearance of untreated and phosfon-treated plants which remained in the greenhouse and of similar ones which received the cool storage is shown in Fig. 1. Exposure to vernalization resulted in limited flowering of the untreated plants and stimulation of a new flush of growth. Plants treated with phosfon and CCC (not shown) produced a cluster of flower buds in place of further vegetative growth. Vernalization stimulated these buds to develop into flowers. Later new vegetative shoots developed at rates inversely proportional to the concentration of the applied retardant.

Earlier trials were made with CCC in June, July, and August of 1960 with plants of five azalea cultivars propagated in 1959. Without exception, application of CCC at rates of 200 ml containing 1580 mg per 5-in. azalea pot, and 250 ml containing 1975 mg per 6-in. pot, suppressed further vegetative growth and induced flower buds to form earlier than they did in untreated plants. The latter produced new shoots at random during the summer. All treated plants bloomed after 4 wk of exposure to a temperature of 10°C. Flowering of treated plants did not occur without exposure to lowered temperatures.

Later trials were made with CCC and phosfon during the winter of 1960–61 with plants of Coral Bells and Alaska cultivars. These plants were lighted 4 hr nightly with 100-watt incandescent filament bulbs to stimulate growth. Unpruned plants continued vegetative growth and those pruned produced new vegetative shoots, whereas those treated with the retardants initiated flower buds at every terminal.

Wittwer and Tolbert (*4*) reported that CCC induced early flowering of tomato. Triiodobenzoic acid is known to induce early formation of flower buds in tomato (*5*), but it is not effective on many other indeterminate plants.

Treatment of azaleas with the two growth retardants removed limitations of plant size and environment for flower initiation. In effect they acted like flower-inducing hormones (florigens), but this is not necessarily the


Fig. 1. (*1*) Branch of plant of *R. obtusum*, cultivar Coral Bells, propagated 25 March 1960 and grown in the greenhouse. (*2*) Branch of similar plant to which 66 mg of phosfon was added 6 October. (3) Branch of similar plant that was grown in the greenhouse until stored at a temperature of 12° to 13°C from 9 November until 21 December and then returned to the greenhouse. (*4*) Branch of plant like (*3*) to which 66 mg of phosfon was added 6 October. Photographed 30 January 1961.

explanation. The substances restricted the growth of the plants, thus presumably altering their metabolism and creating conditions conducive to flower initiation. Growth suppression should result in accumulation of photosynthate which may favor flower initiation, but the action mechanism is probably more involved since pruning of the plants also caused temporary growth restriction but did not result in flower initiation after growth was resumed. The potential importance of controlling flower initiation is obvious and points the way to further investigations (*6*).

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23 February 1961

## Inhibiting Effect of Tobacco Smoke on Some Crystalline Enzymes

*Abstract.* Tobacco smoke absorbed in phosphate buffer at neutral *p*H inhibits irreversibly the enzymes rabbit muscle glyceraldehyde-3-phosphate dehydrogenase and yeast alcohol dehydrogenase, whereas lactic dehydrogenase and glutamic dehydrogenase are not inhibited. A transient inhibition of beef liver catalase occurs. Indirect evidence suggests that the observed enzyme inhibition is caused by peroxides present in the smoke.

In spite of the current interest in the biological effects of smoking, almost no work seems to have been done on the biochemical effects of tobacco smoke. The present finding that tobacco smoke is capable of inhibiting various enzymes may therefore be of interest.

The main-stream smoke from cigarettes, cigars, or pipe tobacco was sucked through 5 ml of phosphate buffer at *p*H 7.4 in a gas absorption flask, and one volume of the smoke solution was subsequently mixed with an equal volume of the enzyme to be tested. In Fig. 1, the effect of cigarette smoke on the SH-enzyme rabbit muscle glyceraldehyde-3-phosphate dehydrogenase is shown. In these experiments the smoke from one nonfilter cigarette was used. It is apparent that the smoke solution is capable of reducing the activity of this enzyme by approximately 65 percent in the course of 30 min. When a 1000-fold molar excess of cysteine was added, a moderate reactivation (approximately 15 percent) was obtained. Similar results were found with cigars or pipe smoke.

Ordinary cigarette filters (cotton-cellulose) were unable to reduce the enzyme inhibition. On the other hand, when the smoke was inhaled and then blown through the absorbing buffer, the inhibition was strongly decreased. The small inhibition obtained in this case (approximately 15 percent) was completely reversed by the addition of cysteine. Thus, the data suggest that the inhibition is caused by two factors. The factor responsible for the irreversible inhibition is apparently removed or destroyed by inhalation.

Similar experiments were carried out with yeast alcohol dehydrogenase, lactic dehydrogenase, glutamic dehydrogenase, and beef liver catalase. Yeast alcohol dehydrogenase ($1.5 \times 10^{-7}M$) was inhibited by approximately 50 percent in the course of 30 min. Lactic dehydrogenase and glutamic dehydrogenase were unaffected. With catalase ($7 \times 10^{-7}M$) a transient inhibition was observed, and its maximum (about 20 percent) occurred after 30 min incubation with the smoke solution. The inhibition was spontaneously and completely reversed within 1 hr.

Previous experiments in this laboratory have demonstrated (*1*) that, when serum albumin is irradiated with x-rays and subsequently added to unirradiated solutions of the SH-enzymes here studied, both rabbit muscle glyceraldehyde-3-phosphate and yeast alcohol dehydrogenase are slowly and irreversibly inhibited, whereas neither lactic nor glutamic dehydrogenase is affected. The inhibition observed under these circumstances has been shown to be due to radiochemically formed peroxides (*2*). The striking similarity between the latter results and those reported above suggested the possibility that the present results might be explained by the presence of peroxides in smoke. Ingram (*3*) has demonstrated the presence of free radicals in smoke condensate, and conceivably, peroxides may be formed upon the reaction of such free radicals with oxygen. However, attempts to determine peroxides by standard micromethods were unsuccessful. The smoke solution formed precipitates with the reagents of the ferric-thiocyanate method (*4*) and the titan-sulfate method (*5*). With the iodine method (*6*) no peroxides could be demonstrated, even when bottle hydrogen peroxide was added to the smoke solution. The possibility that the added peroxide was dissipated in reactions with constituents of the smoke solution was excluded by the findings that the addition of bottle hydrogen peroxide led to the expected increase in the inhibition of the rabbit muscle dehydrogenase, and that catalase readily abolished this additional inhibition. Presumably iodine formed in the oxidation by peroxides is consumed in reactions with unsaturated hydrocarbons in the smoke solution.

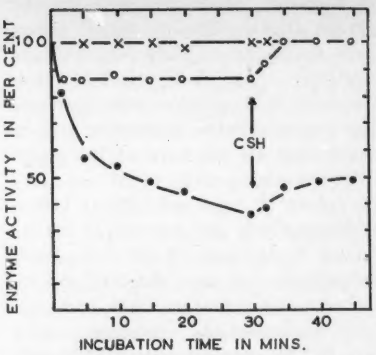


Fig. 1. Inhibition of rabbit muscle glyceraldehyde-3-phosphate dehydrogenase by cigarette smoke. The enzyme ($10^{-6}M$) in $0.067M$ phosphate buffer, *p*H 7.4, at 0°C was mixed with an equal volume of a buffer solution of cigarette smoke. Cysteine (CSH) in a final concentration of $5 \times 10^{-4}M$ was added after 30 min. Solid circles: cigarette smoke absorbed directly in buffer; open circles: cigarette smoke inhaled prior to absorption in buffer; crosses: control (buffer).

Since chemical methods did not provide any direct proof for the existence of peroxides in the smoke solution, some experiments have been performed in order to obtain indirect evidence for the role of peroxides in the enzyme inhibition by tobacco smoke. Thus, when different compounds were added to the absorbing buffer *prior* to the smoking procedure, it was found that thiols in high concentration ($5 \times 10^{-6}M$) abolished completely the inhibition of the rabbit muscle dehydrogenase, whereas ethylene diaminetetraacetic acid had only a moderate effect. Furthermore, when the smoke solu-

tion was incubated for half an hour with catalytic amounts of catalase ($7 \times 10^{-10} M$) before mixing with the enzyme solution, no inhibition of the rabbit muscle dehydrogenase was observed. These results, which are in close agreement with those obtained when the inhibiting effect of irradiated protein solutions was studied, are clearly consistent with the proposed peroxide mechanism. The transient inhibition of catalase is also compatible with this mechanism, as a transient formation of inactive catalase-peroxide complexes is observed when catalase is added to an excess of perodixes (*7*).

It appears that, irrespective of the underlying mechanism, the present finding that tobacco smoke inhibits various enzymes, and that inhalation apparently removes or destroys the inhibitor, may be of biological interest (*8*).

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24 March 1961

## Response of Condylar Growth Cartilage to Induced Stresses

*Abstract*. The endochondral growth apparatus of the mandibular condyles, in contrast to epiphyseal plates of long bones, reacts positively to mechanical stimulation. Roentgenographic and histologic analyses of the joint structures of two experimental rhesus monkeys, when compared with untreated controls, showed obvious morphologic and structural transformations of the condylar heads as the result of the instituted treatment. Corollary differences were found in the ontogenetic and histogenetic pattern, as well as in the hormonal control, of these condylar growth centers.

Experiments by Strobino *et al.* on calf tibias (*1*) and the clinical experiences of Blount and Zeier (*2*) with unsuccessfully splinted long bones of children indicated that, contrary to Wolff's law and Roux's principle of functional bone transformation, epiphyseal cartilage plates remain highly unresponsive to mechanical stimuli. Fell (*3*) concluded from findings in tissue cultures that the "gross morphology of bone tissue depends much more upon environmental influences than does that of cartilage." On the other hand, we have presented histologic evidence that in an infant with micrognathia (Robin's syndrome) the condylar cartilage responded to functional treatment with a corrective growth spurt (*4*).

In view of reports of self-corrections of this condition (*5*), an experiment in three rhesus monkeys aged 44 to 50 mo was designed to assess condylar response to induced stresses.

Monkey I served as untreated control, and monkeys II and III as the experimental animals. Inclined bite planes were cemented on the upper and lower dental arches so that the mandible upon occlusion was guided into a forward position. The forces applied thus were physiologic but parafunctional. Monkey II was killed after 2½ mo of treatment; monkey III was autopsied after 4½ mo of the experiment.

Both experimental monkeys show obvious changes in the gross morphologic and roentgenographic appearance of the condylar head (Fig. 1). Histologically the structural arrangement of the condylar head, compared with the normal control (Fig. 2), shows increased cartilage proliferation in a backward and upward direction; endochondral ossification is most active in the posterior portion (Fig. 3). Since modeling resorption at the anterior surface lagged behind proliferation at the posterior surface, the condyles assumed a bilobed shape (Fig. 4). These growth processes result in a bend of the condyles toward the fossa as if they were returning to the position before treatment.

Thus, concrete evidence is obtained which shows that the condylar growth center responds to functional therapy. This unique behavior of condylar cartilage is accompanied by some peculiarities in development, histologic structure, endochondral ossification, and its hormonal control, which differ from the pattern of epiphyseal growth centers:

1) All epiphyseal plates of long bones are derivatives of the primordial cartilage skeleton; the condylar cartilage develops independently from it as a so-called secondary cartilage "grafted" upon the mandibular membrane bone (*6*).

2) Epiphyseal plates grow interstitially; condylar cartilage accrues by surface apposition in a peripheral fibrocartilage layer.

3) In contrast to other cartilage bones, no secondary ossification centers are formed in the condyles. Maturation

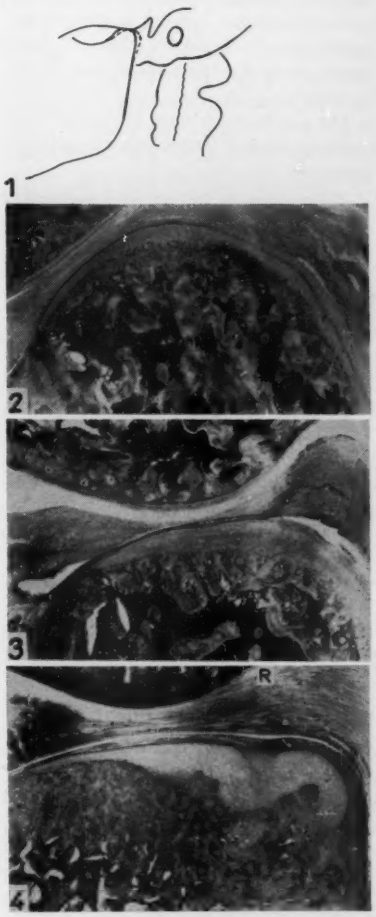


Fig. 1. Superposed tracings of the roentgenocephalograms of the temporomandibular joint structures of experimental monkey III at the beginning of experiment upon insertion of a fixed mandibular protractor appliance, and after 4½ mo of treatment (stippled), reveal that upon treatment the condyle has assumed an oviform shape and is dorsally more prominent with respect to the posterior border of the ramus. The circumferences of the mandibular angle and temporal joint structures are unchanged. Fig. 2. Sagittal section of joint structure of control monkey I. (Alizarin-S vital-staining had unfavourable effect upon histodifferentiation.) Fig. 3. The condyle of experimental monkey II after 2½ mo of treatment shows increased size through cartilage proliferation in a caudal direction. Fig. 4. The condyle of experimental monkey III after 4½ mo of treatment exhibits a prolonged, bilobed shape. *R*, resorbtion.

never occurs; the cartilage persists through life, and it is never completely eroded nor sealed off as are the epiphyseal plates.

4) Endocrine experiments in rats have revealed differences in the hormonal control of growth activity between the epiphyseal plates and the condylar heads. After thyroidectomy, growth hormone elicited a greater response in the condyles than in long bones, while the latter responded better to thyroxin (*7*).

The condylar cartilage holds a unique position among endochondral growth centers.

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23 January 1961

## Blood Trehalose and Flight Metabolism in the Blowfly

*Abstract.* The concentration of trehalose in the blood of *Phormia regina* was found to determine the rate of energy expenditure during flight as reflected in measurements of the wing-beat frequency. Fat body was found to be the source of blood trehalose; either endogenous or exogenous substrates are used for its synthesis.

The function of the nonreducing disaccharide, trehalose, in insect blood has been the subject of a number of studies (*1*). In the adult blowfly, *Phormia regina* (Meig.), it has been found previously that trehalose is the main carbohydrate in the blood (up to 3 g/lit.), that glucose also is present but at much lesser concentrations, that both sugar concentrations are a function of nutrition, and that trehalose concentration falls during flight (*2*). We have since examined this last point in more detail and have sought the source of blood trehalose.

For flight, males were maintained on 1*M* glucose for 4 to 5 days after eclosion and then mounted by a thin support glued to the dorsum of the abdomen. To promote flight, the tarsi were removed (*3*). About 60 percent of such flies flew regularly for long periods; these flies were selected for study. The wing-beat frequency, shown to be a reliable measure of the rate of energy expenditure (*4*), was measured stroboscopically. Blood carbohydrates were assayed chromatographically and colorimetrically as before (*2*).

The wing-beat frequency fell during prolonged flight, as reported by others (*5*, *6*), and blood trehalose fell with it (Fig. 1); blood glucose did not change significantly. The duration of flight to exhaustion was 2 to 3 hr. These results suggested that substrate availability might directly determine the wing-beat frequency, since it has been shown that, after flight to exhaustion, feeding of suitable carbohydrates can bring about almost immediate resumption of flight for long periods (*7*). Accordingly, the effect of trehalose injections on the wing-beat frequency was measured over the physiological range of the frequency.

Flies were flown to complete exhaustion (*7*), and the wing-beat frequency at which they stopped was designated as the "exhausted wing-beat frequency." Each fly was then injected serially with 52, 105, and 210 $\mu$g of trehalose dissolved in saline. In all cases 0.524 $\mu$l (standard error, $\pm$0.008) was injected through a fine glass needle on a microinjection apparatus. After each injection, the fly was rested for a 3-min equilibration period and then flown. The wing-beat frequency was recorded every 10 sec for the first minute of flight; then these values were averaged and designated as the wing-beat frequency after injection. The flies were again flown to exhaustion after each injection. After the last injection, each fly was fed 2*M* glucose to repletion, rested for 30 min and flown again. The wing-beat frequency thus obtained was designated as the wing-beat frequency after feeding. This value may be considered as the maximum for a given fly.

Table 1 summarizes the results of these experiments. Clearly, the injections of trehalose did increase the wing-beat frequency, and the amount of the increase over the level at exhaustion was directly related to the amount of trehalose injected. The greatest amount (210 $\mu$g) restored the wing-beat frequency to the level found after feeding. These results indicate that the wing-beat frequency under these conditions was determined by the concentration of

Table 1. Wing-beat frequency (WBF) as a function of blood trehalose administered by injection. Each exhausted fly was serially injected with the three quantities of trehalose, in the same volume of saline, and re-exhausted between injections. The "fed" value was obtained from the same flies after the last injection by feeding to satiation and resting for 30 min.

| Treatment | Mean WBF (cy/min) | % |
|---|---|---|
| Exhausted | 7,460 | 67 |
| Injected | | |
| 52 $\mu$g | 8,800 | 79 |
| 105 $\mu$g | 9,750 | 88 |
| 210 $\mu$g | 10,950 | 99 |
| Fed | 11,020 | 100 |

trehalose available to the flight muscles. Glycogen in flight muscle undoubtedly is also an important energy source, and its concentration has been related to the wing-beat frequency in *Drosophila* (*5*).

*Phormia regina* has been estimated to expend carbohydrate during flight at a rate of about 15 $\mu$g/min (*8*). At this rate the total amount of trehalose in the blood (about 200 $\mu$g maximum) could support flight for only a few minutes unless it was continually being replaced. The origin of blood trehalose was therefore a question of considerable interest. Fuel for the flight of Diptera comes in large part from glycogen stored in the fat body (*7*,

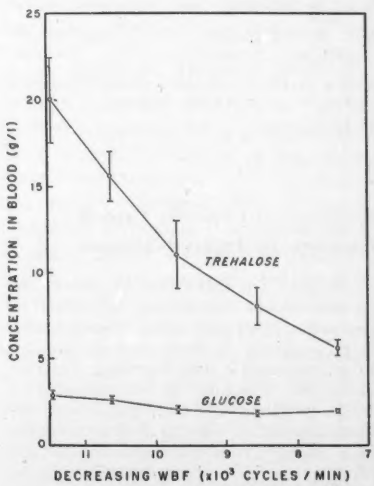


Fig. 1. Relationship between the wing-beat frequency (WBF) and the concentration of blood glucose and trehalose. The data were grouped by averaging observations of wing-beat frequency (at least 10 individual ones per point) made over intervals of 1000 cy/min from 12,000 to 7000 cy/min (which is approximately the exhausted frequency). The standard error of the mean (bars) was calculated for the sugar concentrations.

8, 9), and blood trehalose obviously might be the transport form of this glycogen. Fat-body extracts of locust do synthesize trehalose from glucose (10). When the fat body of *Phormia* was examined, it was found that intact cells in vitro "secreted" trehalose into the medium at rates up to 300 μg/mg (dry wt.) per hour. In view of the observations listed above, and since four analyses of fat body showed trehalose concentrations of less than 26 μg/mg (dry wt.), glycogen is probably the main source of this trehalose. That the fat body can also synthesize trehalose from exogenous glucose and release it into the medium was demonstrated by incubating intact fat body with glucose-U-$C^{14}$ having a specific activity of 2620 count/min per micromole. Trehalose isolated from the medium after 30 min of incubation had a specific activity of 822 counts/min per micromole, and this accounted for 93 percent of the total counts, other than glucose, found in the medium. Preparations of midgut, flight muscle, and blood were unable to produce trehalose when assayed in this way.

The present results (11) and other observations (12) lead to the conclusion that the fat body produces trehalose during flight and that the concentration of this sugar in the blood determines, at least in part, the rate of energy expenditure by the flight muscles. This finding complements Sacktor's views of the regulation of flight-muscle metabolism (1).

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12. A paper describing the relationships between energy sources in fat body, blood, and muscle is in preparation.

20 February 1961

## Long-Term Nontoxic Support of Animal Life with Algae

*Abstract.* One 40-g male albino mouse was kept in good health for 66 days in a chamber containing an algal photosynthetic gas exchanger. Carbon dioxide was well controlled, oxygen was slowly increased, and nitrogen was decreased in the chamber. Photosynthesis can support life in a hostile environment for extended periods of time.

One method of reducing the weight of the contents of an inhabited space capsule or vessel for long voyages in a hostile environment is to recycle the constituents of the initial load, utilizing solar energy to reverse the entropy-increasing reactions required for living. Such recycling is done on a much larger scale on the earth's surface, where chlorophyll-containing plants use waste $CO_2$ from animals, decay, and combustion to create food and fuels, and to restore $O_2$.

Photosynthetic gas exchangers are of use in life-support systems. Unicellular plants or algae have been used with animals because they are efficient in the use of light, they can be cultured in relatively simple liquid media, and they produce little fiber or nonfood material. The algae take up $CO_2$ and give off $O_2$; the animal in the system uses $O_2$ and produces $CO_2$ which regulates the growth of the algae. In theory, when the respiratory quotient of the animal is the same as the assimilation quotient of the plant, a stable state is reached.

Myers maintained mice for various periods of time by gas regeneration with algae (1). The U.S. Air Force School of Aerospace Medicine has supported various animals, including monkeys (2), on algae for short periods of time. At the Chance Vought Research Center mice have been maintained for as long as 28 days (3). A 66-day run was completed successfully in August 1960.

The apparatus used was described previously (3). The algal chamber contained 4 liters of 1 percent packed cell volume of Sorokin thermophilic strain of *Chlorella pyrenoidosa* (4). The mouse chamber was a Scheibler desiccator, 250 mm in diameter, containing vermiculite bedding, a supply of Purina food pellets, and a supply of water. Air was circulated from the mouse chamber through the algal culture at 39°C; it was dehumidified by a condenser cooled to 5° to 15°C and returned to the mouse chamber. The algal culture received 300 ft-ca of fluorescent light on its outer surface and about 400 ft-ca on its inner surface; the culture thickness was ¾ in. The algal medium was that recommended by Myers (3). It was made from Knops-urea, microelements, iron sulfate, and ethylenediamine tetraacetate as chelating agent and adjusted to *p*H 6.8 with 2*N* potassium hydroxide. One drop of Silicone Antifoam A was added to new medium occasionally to prevent foaming of the culture. The medium was harvested and replenished by adding fresh medium from a separatory funnel at the top of the algal chamber at the same time that the culture was withdrawn from the bottom with the pump turned off. A water manometer was watched so that pressure in the system was maintained with minimal change during, and with no change after, harvesting.

A male mouse, weighing 38.9 g, about 1 year old, was sealed up in the desiccator at noon on 7 June 1960. Leaks in the system were sought with a soap solution, and none were found; later checks were also negative. Harvesting and replacement of the medium was done each Monday, Wednesday, and Friday. The packed cell volume of the algae was kept between 0.6 and 1.7 percent and usually varied from 0.7 percent after harvest to 1.3 percent before. A total of 53 liters of algae were removed during the experiment; this contained approximately 131 g of air-dried algae. After the system was opened on 12 August at 3 P.M., there was about 200 ml more of algal culture than there had been at the start. Since 400 ml of gas were removed for analysis, and since the food and water consumed occupied some space, these decreases in the total gas volume in the system must be balanced by the extra culture fluid and also by added gases in the medium admitted at 28°C and by removed gases in the culture at 39°C. The total gas volume was estimated at 5 liters. Room temperature was stabilized by air-conditioning at 28° ± 1°C.

Gas was removed from the latex rubber tubing to the mouse chamber with a hypodermic needle and syringe. On 19 occasions, three times weekly at first and once weekly later, samples of 20 to 22 ml of system gas were analyzed in duplicate, within 2 hr, on a Perkin-Elmer gas chromatograph standardized with known gas mixtures and controlled each time with room-air analyses. A silica gel column and 1-ml samples were used for $CO_2$; a molec-

ular sieve column and 0.25-ml samples were used for $O_2$. At the start of the experiment the chamber air contained 0.4 percent $CO_2$ and 21 percent $O_2$. Before the chamber was opened on the last day, it contained 0.13 percent $CO_2$ and 63 percent $O_2$. Oxygen had slowly accumulated to 21.5 percent after 1 day, 23.5 percent after 3 days, 26 percent after 8 days, 34 percent after 13 days, 40 percent after 17 days, 43 percent after 30 days, 53 percent after 40 days, 55 percent after 48 days, and 58 percent after 61 days. Carbon dioxide was well controlled, usually being analyzed at 0.2 percent or less. Only one analysis exceeded 0.8 percent (31st day). A value of 5 percent was obtained on the 28th day, after a weekend when algal growth had attained 1.7 percent packed cell volume. The mouse did not show respiratory signs or lack of activity consistent with this high value. Analysis had shown 0.2 percent $CO_2$ on the 24th day, so the analysis was considered to be in error for unknown reasons.

At no time were gas chromatograph peaks for methane or ethane seen. The chamber contents were checked for CO with the Mine Safety Appliances analyzer at the end of the experiment, and no accumulation of CO was found. Both room air and chamber gas were alike, containing less than 0.001 percent CO. The CO reached toxic levels in blue-green algal gas exchangers (*5*).

The mouse was normally active, though confined, throughout the run. It weighed 43.5 g when removed, a weight gain of 4.6 g. It remained healthy for more than 9 months after the experiment. The increased $O_2$ in the atmosphere (30 percent rising to 60 percent over a period of 50 days) and restoration to 21 percent had no adverse effect.

Odor in the mouse chamber containing the accumulated excreta of 66 days was considerably less than that of an uncleaned cage after 1 week. This is explained by the fact that relatively dry air entered the chamber and by the deodorant action of the algal culture. No activated charcoal or other absorbent was used. Ammonia, volatile fatty acids, hydrogen sulfide, and mercaptans would be metabolized and removed by the algae. Chlorophyll has also been claimed to be a deodorant.

No precautions were taken to begin with or to maintain a pure culture of *Chlorella*. Bacteria were present, but created no problem. Fecal bacteria in a previous experiment (*3*) had demonstrated that their aerobic metabolism can disrupt the functioning of the system. Close to 400 ml of tap water were used by the mouse, except for a slight loss by wastage and evaporation. Exhaustion of this supply was the reason for terminating the experiment.

The variation in chamber $N_2$ is unexplained. With the rise in $O_2$ and the maintenance of $CO_2$, the $N_2$ decreased progressively. Nitrogen storage in the mouse's weight gain could explain a very small part of the decrease. It is estimated that about 2 liters of $N_2$ disappeared from the chamber air. Removed culture should have contained less than the added medium because the temperature change reduced the nitrogen's solubility. Undetected leaks should also have the effect of increasing low values of $N_2$. *Chlorella* does not fix $N_2$. Bacteria could, but this seems to be a large amount of nitrogen fixation, and in other experiments no evidence for nitrogen fixation has been found. The oxygen buildup can be explained by imbalance in the respiration quotient of the mouse and the assimilation quotient of the algae. This could be prevented by use of ammonium salts as the nitrogen supply in the medium, and such an experiment might supply an answer to the $N_2$ picture.

One minor accident occurred on the 22nd day. While the medium was being admitted, the separatory funnel was inadvertently emptied, and room air estimated to be 100 ml or less entered the chamber. This would be 2 percent or less of room air added to chamber air of 0.2 percent $CO_2$, 40 percent $O_2$, and 59.8 percent $N_2$.

An average man's weight is three orders of magnitude greater than that of this rather large mouse. The respiratory exchange is two orders of magnitude higher. The present experiment indicates 100 gallons of 1 percent packed cell volume of algae could support life for one man. The lighting was designed for the standard strain of *Chlorella*. Optimum lighting for the thermophilic strain is much higher (*6*). Improved performance can be developed even in the absence of gravity where the separation of gas from liquid is a problem. Relatively long-term safety and reliability have been shown for this system.

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24 January 1961

## Diageotropism in Vanilla Roots

*Abstract.* Diageotropic growth in the dark and geotropic growth in the light occurred in the roots of cuttings of three *Vanilla* species. The diageotropic response also occurred in far-red, red, orange, and green light, while positive geotropism resulted only if blue light was present.

Diageotropism, or the orientation of plant parts at right angles to the direction of gravity, was mentioned by Darwin (*1*) as occurring in certain rhizomes and probably in some secondary roots. Bennet-Clark and Ball (*2*) reported that the diageotropic response of the rhizome of *Aegopodium* occurred only in the absence of light and that positive geotropism occurred in the presence of light of any color. They suggested that growth curvatures in response to light and darkness served as a depth-regulating mechanism. A search of the available literature did not reveal reports of a similar light-dependent mechanism in roots, or of a plant with a diageotropic terrestrial roots system.

The pendent roots of *Vanilla* vines may grow downward as far as 30 ft before reaching the ground. After they reach the ground, the roots turn at right angles and ramify through the accumulated organic matter and seldom penetrate the mineral soil. Although the physical resistance of the soil may be a factor in controlling root growth, recent work at this station indicates that light may play a major role in determining the direction of growth of *Vanilla* roots.

To determine the effect of light on root growth, single-node cuttings of *Vanilla planifolia* Andrews with at-

tached leaves were rooted under intermittent mist spray. After they were selected for uniformity, cuttings with adventitious roots were placed in 1-gallon glass chambers with a relative humidity of 100 percent. The direction of the root tips was recorded at that time. Replicate chambers were exposed to fluorescent light (500 ft-ca) for 9 hr daily, and additional chambers were maintained in continuous darkness. All chambers were opened daily to allow a brief circulation of air.

The roots of plants exposed to light responded rapidly to the stimulus of gravity. Figure 1 shows the positive geotropism that occurred in illuminated roots regardless of the original direction of the tips. The root tips responded faster when oriented directly upward than when oriented horizontally. The curvature could be detected 3 hr after positioning; in 20 hr the root tips completed a curvature of 180°.

Cuttings, which had been kept in darkness for a 2-day conditioning period and which were then oriented with tips up and retained in darkness, made initial growth responses in approximately the same time as those grown in light. However, after the root tips had turned 90° from the vertical, this response invariably halted. Growth in a horizontal plane continued for 10 days if the plants remained in darkness. Roots placed in a horizontal position continued to grow in that plane, while roots originally down required 12 hr to turn toward the horizontal (Fig. 2).

Fig. 1. Light-induced geotropic response in roots of *Vanilla planifolia*. The cut portion of the roots indicates the original basipetal position.

In other tests the chambers were wrapped with colored and clear cellophane to provide illumination by far-red, red, orange, green, blue, and white light. Cuttings were placed in the chambers, and the lighting was arranged to provide a similar light intensity (15 ft-ca) in each container. A consistent diageotropic response occurred after the root tips remained for 48 hr in far-red, red, orange, and green light. Positive geotropism resulted only in those roots maintained in blue and in white light.

Some photic responses may be initiated by the absorption of light in the blue region of the spectrum by carotenoids (*3*) or caroteno-protein (*4*). We extracted 50 root tips with acetone and obtained a mixture of two yellow pigments. The mixture was separated on filter paper with hexane as the solvent. Spectrophotometric curves obtained from the eluted pigments indicated that they were beta-carotene ($A_{max}$ at 425, 451, and 480 m$\mu$) and lutein ($A_{max}$ at 419, 447, and 477 m$\mu$). These data are compatible with the concept that the absorption of blue light by carotenoids mediates the positive geotropic response of *Vanilla* roots.

Responses to applications of indoleacetic acid by roots grown in darkness suggest that the diageotropic growth was not due to a complete loss of sensitivity to auxin. Applications of indoleacetic acid (1, 10, and 100 parts per million in lanolin) to a point 1 mm from the root apex resulted in pronounced growth curvatures toward the site of application. Applications of indoleacetic acid to roots grown in light resulted in similar curvatures. Lanolin alone was ineffectual in roots grown in both darkness and light. The growth rate of roots in both treatments was approximately 5 mm a day for the first 6 days.

Rooted cuttings of *V. dilloniana* Correl, *V. phaeantha* Reichb. f, and a hybrid between *V. planifolia* and *V. phaeantha* responded to light and dark treatments in a manner similar to *V. planifolia*. The aerial roots of two other semi-epiphytic, climbing orchids, *Vanda* sp. and *Aerides* sp., failed to respond to the gravitational stimulus in this experiment.

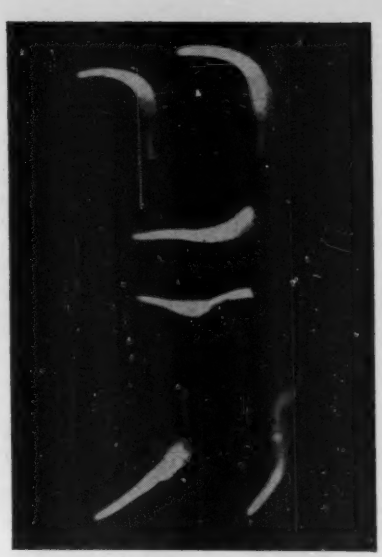

Fig. 2. Dark-induced diageotropic response in roots of *Vanilla planifolia*. The cut portion of the roots indicates the original basipetal position.

The geotropic response of *Vanilla* roots may be separated into two phases. The first consists of the curvature of the roots from the vertical (tip up) to the horizontal, the response to gravitational stimulus occurring both in light and in the dark. The second, occurring in the presence of blue light, is the curvature of the root from the horizontal to the vertical, but with the tip down. The effects of the light-induced curvature in the second phase may be reversed in the absence of blue light, resulting in an upwards curvature of the root and the resumption of the diageotropic position.

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**References**

1. C. Darwin, *The Power of Movement in Plants* (D. Appleton, New York, 1896).
2. T. A. Bennet-Clark and N. G. Ball, *J. Exptl. Botany* **2**, 169 (1951).
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26 May 1961

# Meetings

## Forthcoming Events

### July

*31–4.* American Crystallographic Assoc., Boulder, Colo. (W. M. Macintyre, Univ. of Colorado, Boulder)

*31–4.* Biophysics, 1st intern. congr., Stockholm, Sweden. (B. Lindström, Dept. of Medical Physics, Karolinska Institutet, Stockholm 60)

*31–4.* Differential Equations in Non-Linear Mechanics, Air Force Acad., Colorado Springs, Colo. (J. P. Lasalle, 7212 Bellona Ave., Baltimore 12, Md.)

*31–11.* Physics of the Solar System and Re-entry Dynamics, conf., Blacksburg, Va. (Bureau of Public Relations, Virginia Polytechnic Inst., Blacksburg)

*31–12.* Electric Power and Problems of Nuclear Power, seminar, U.N. Economic Commission for Latin America, Mexico, D.F. (A. Dorfman, Chief, Energy and Water Resource Program, Avenue Providencia 871, Santiago, Chile)

### August

*1–15.* Pan American Inst. of Geography and History, 7th general assembly, Buenos Aires, Argentina. (I. Marquina, Secretary General, Instituto Panamericano de Geografia e Historia, Ex-Arzobispado 29, Mexico 18, D.F.)

*1–26.* Functional Analysis, 8th American Mathematical Soc. summer institute, Stanford, Calif. (P. D. Lax, AMS, 190 Hope St., Providence 6, R.I.)

*2–5.* International Conf. of Pure and Applied Chemistry, 21st, Montreal, Canada. (R. Morf, Hoffmann-LaRoche, S.A., Grenzachterstrasse 124, Basel, Switzerland)

*3–5.* Canadian Chemical Conf. and Exhibition, 44th, Montreal. (Chemical Inst. of Canada, 48 Rideau St., Ottawa 2, Ont.)

*4–5.* Pennsylvania Acad. of Science, 36th summer, Grove City. (J. J. McDermott, Franklin and Marshall College, Lancaster, Pa.)

*5–9.* International Rorschach Soc., 5th congr., Fribourg-en-Brisgau, Germany. (A. Friedemann, Chemin des Pêcheurs 6, Bienne, Switzerland)

*6–10.* Occupational Medicine and Toxicology, 3rd Inter-American conf., Miami, Fla. (W. B. Deichmann, School of Medicine, Univ. of Miami, Coral Gables, Fla.)

*6–12.* Atmospheric Ozone and General Circulation, symp., Arosa, Switzerland. (H. U. Duetsch, 20 Carl Spittelerstrasse; Zürich 53, Switzerland)

*6–12.* Chemical and Thermodynamic Properties at High Temperatures, symp., Montreal, Canada. (N. F. H. Bright, Natl. Research Council, Ottawa, Canada)

*6–12.* International Congr. of Pure and Applied Chemistry, 18th, Montreal, Canada. (L. Marion, Natl. Research Council, Ottawa 2, Canada)

*7–9.* Guidance and Navigation Conf., American Rocket Soc., Palo Alto, Calif. (J. J. Harford, ARS, 500 Fifth Ave., New York, N.Y.)

*7–9.* International Committee of Electro-Chemical Thermodynamics and Kinetics, 13th meeting, Montreal, Canada. (N. Ibl, Eidg. Technische Hochschule, Laboratorium für Physikalische und Elektrochemie, Universitätsstrasse 6, Zürich 6, Switzerland)

*7–9.* Space Age Astronomy, intern. symp., Pasadena, Calif. (D. W. Douglas, Jr., Douglas Aircraft Co., Inc., Santa Monica, Calif.)

*7–10.* National Medical Assoc., New York, N.Y. (J. T. Givens, 1108 Church St., Norfolk, Va.)

*7–11.* High Temperature Chemistry and Thermodynamics, symp., Montreal, Canada. (L. Brewer, Dept. of Chemistry, Univ. of California, Berkeley)

*7–11.* Seminar on Fast and Intermediate Reactors, International Atomic Energy Agency, Vienna, Austria. (IAEA, 11 Kärtner Ring, Vienna 1)

*8–11.* Poultry Science Assoc., State College, Pa. (C. B. Ryan, Texas A & M College, College Station)

*8–16.* Society of Protozoologists, Prague, Czechoslovakia. (N. D. Levine, College of Veterinary Medicine, Univ. of Illinois, Urbana)

*10–16.* International Congr. of Biochemistry, 5th, Moscow, U.S.S.R. (N. M. Sissakian, Leninsky prospekt, 33, Moscow)

*10–16.* International Union of Biochemistry, 4th general assembly, Moscow, U.S.S.R. (R. H. S. Thompson, IUB, Dept. of Chemical Pathology, Guy's Hospital Medical School, London, S.E.1, England)

*12–19.* Fast Reactions, summer school, Cambridge, England. (Secretary of the Summer School, Dept. of Physical Chemistry, Lensfield Road, Cambridge)

*13–18.* Microchemical Techniques, intern. symp., University Park, Pa. (H. J. Francis, Jr., Pennsalt Chemical Corp., P.O. Box 4388, Chestnut Hill Post Office, Philadelphia 18, Pa.)

*13–18.* Theoretical Aspects of Magnetohydrodynamics, seminar, University Park, Pa. (Conference Center, Pennsylvania State Univ., University Park)

*13–19.* International Assoc. of Applied Psychology, 14th congr., Copenhagen, Denmark. (Congress Secretariat, 19 Sankt Pederstraede, Copenhagen K.)

*13–19.* Training for Research in the Processes of Vision, 1st intern. conf., Rochester, N.Y. (Office of Public Information, River Campus Station, Rochester)

*14–17.* Calorimetry Conf., intern., Ottawa, Canada. (J. E. Kunzler, Bell Telephone Laboratories, Murray Hill, N.J.)

*14–19.* International Medical Conf. on Mental Retardation, 2nd, Vienna, Austria. (Miss E. Langer, Div. of Maternal and Child Health, State House, Augusta, Maine)

*14–19.* Symposium on Radiation, Vienna, Austria. (World Meteorological Organization, 1 Avenue de la Paix, Geneva, Switzerland)

*14–25.* Israel Medical Assoc., 5th world assembly, Jerusalem, Israel. (Beth-Harofeh, 1 Heffman St., Tel-Aviv, Israel)

*14–26.* Plant Pathology, conf., Lafayette, Ind. (J. F. Schafer, Dept. of Botany and Plant Pathology, Purdue Univ., Lafayette)

*14–26.* World Eucalyptus Conf., 2nd, São Paulo, Brazil. (Intern. Agency Liaison Branch, Office of the Director General, Food and Agriculture Organization, Viale delle Terme di Caracalla, Rome, Italy)

*15–17.* International Assoc. of Milk and Food Sanitarians, Jekyll Island, Ga.

# Kodak reports on:

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**1.** Years ago we threw our weight on the side of the angels by a Good Deed. We went to work for the astronomers, a group noted for the slimness of their budgets. We made them the special photographic plates needed for all the projects that have seemed pressing to them, like measuring the angular momentum of galaxies. This work has netted us a medal or two but no wealth. That's all right. Questions about these plates are answered by Eastman Kodak Company, Special Sensitized Products Division, Rochester 4, N. Y. Professional astronomers know that address very well.

**2.** Amateur astronomers are among the most numerous of scientific-type hobbyists. Many thousands of persons who have to deal all day with tiresome human affairs like to reach out toward the ultimate verities through a backyard telescope. But, being human themselves, they hanker for tangible trophies of the sport. These photography can provide. To guide, we provide a free booklet, "Astrophotography with Your Camera," from the same address the professionals know. The amateur astronomers far outnumber the professionals and buy standard Kodak films at popular prices.

**3.** A protostar evolving from clouds of dust a million light-years away and an ICBM a thousand miles from the U. S. border have a certain resemblance in the infrared. At Ohio State University we have some astronomers working for us on an astronomical job which lack of suitable equipment has long delayed—preparation of an atlas of infrared emitters on the celestial sphere to 13.5 microns. We made them the missing equipment. We need the atlas. We have our reasons. The equipment includes a drift-free homodyne amplifier which takes a signal from our liquid-helium-cooled copper-doped germanium detector on the 69-inch Perkins Observatory telescope. It can cramp down to a .0011 cycle/sec scanning bandwidth so that in 20 minutes it can distinguish the emission of a single star from intergalactic infrared noise. Those who have need and funds for such up-to-date infrared systems should get in touch with Eastman Kodak Company, Apparatus and Optical Division, Rochester 4, N. Y.

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(H. L. Thomasson, P.O. Box 437, Shelbyville, Ind.)

*15–18.* Technical Assoc. of the Pulp and Paper Industry, 12th testing conf., Montreal, Canada. (TAPPI, 155 E. 44 St., New York 16)

*15–24.* International Astronomical Union, 11th general assembly, Berkeley, Calif. (D. H. Sadler, Royal Greenwich Observatory, Hailsham, Sussex, England)

*16–18.* Hypersonics Conf., intern., Cambridge, Mass. (J. J. Harford, American Rocket Soc., 500 Fifth Ave., New York, N.Y.)

*18–21.* Association of American Geographers, East Lansing, Mich. (M. F. Burrill, 1785 Massachusetts Ave., NW, Washington 6)

*19–30.* Agricultural Economists, 11th intern. conf., Cuernavaca, Mexico. (J. Ackerman, Farm Foundation, 600 S. Michigan Ave., Chicago, Ill.)

*20–23.* International Ergonomics Assoc., 1st congr., Stockholm, Sweden. (T. Olson, Dept. of Industrial Physiology, G.C.I. Lidingövägen 1, Stockholm)

*20–24.* American Veterinary Medical Assoc., Detroit, Mich. (H. E. Kingman, AVMA, 600 S. Michigan Ave., Chicago 5, Ill.)

*21–23.* International Hypersonics Conf., Cambridge, Mass. (F. Ridell, Avco Research Laboratory, 301 Lowell St., Wilmington, Mass.)

*21–24.* Biological Photographic Assoc., Chicago, Ill. (Mrs. J. W. Crouch, Box 1668, Grand Central P.O., New York 17)

*21–24.* International Conf. on Photoconductivity, Ithaca, N.Y. (E. Burstein, Dept. of Physics, Univ. of Pennsylvania, Philadelphia)

*21–26.* International Congr. of Psychotherapy, 5th, Vienna, Austria. (W. Spiel, Lazarettg. 14, Vienna 9)

*21–26.* World Traffic Engineering Conf., Washington, D.C. (Intern. Road Federation, 1023 Washington Bldg., Washington 5)

*21–27.* International Assoc. of Dental Students, congr., London, England. (D. H. Clark, Royal Dental Hospital, Leicester Sq., London, W.C.2)

*21–31.* United Nations Conf. on New Sources of Energy, Rome, Italy. (United Nations, New York, N.Y.)

*21–2.* International Congr. of Practical Medicine, Merano, Italy. (Bundesärtztekammer, 1 Hädenkampfstrasse, Cologne, Germany)

*21–6.* Pacific Science Congr., 10th, Honolulu, Hawaii. (Secretary General, 10th Pacific Science Congr., Bishop Museum, Honolulu)

*22–25.* International Pharmacological Meeting, 1st, Stockholm, Sweden. (A. Wretlind, Karolinska Institutet, Stockholm 60)

*22–30.* International Conf. on Protozoology, Prague, Czechoslovakia. (N. D. Levine, College of Veterinary Medicine, Univ. of Illinois, Urbana)

*23–25.* Gas Dynamics, symp., biennial, Evanston, Ill. (J. J. Harford, American Rocket Soc., 500 Fifth Ave., New York, N.Y.)

*23–26.* Electron Microscope Soc. of America, Pittsburgh, Pa. (Miss M. L. Rollins, Agricultural Research Service, U.S. Department of Agriculture, P.O. Box 19,687, New Orleans 19, La.)

*23–26.* Institute of Management Sciences, 8th annual intern., Brussels, Belgium. (W. Smith, Inst. of Science and Technology, Univ. of Michigan, Ann Arbor)

*23–1.* Radioisotopes in the Biological Sciences, conf., Intern. Atomic Energy Agency, Vienna, Austria. (IAEA, 11 Kärtner Ring, Vienna 1)

*24–26.* Physiology of the Hippocampus, intern. colloquium, Montpellier, France. (Mme. Mineur, Centre National de la Recherche Scientifique, 13 Quai Anatole France, Paris 7)

*26–1.* Radiology, 10th intern. congr., Montreal, Canada. (C. B. Peirce, Suite 204, 1555 Summerhill, Montreal 25)

*26–2.* History of Science, 5th intern. congr., Ithaca, N.Y., and Philadelphia, Pa. (Secretary, 5th Intern. Congress of the History of Science, Cornell Univ., Ithaca)

*27–29.* International Congr. of Group Psychotherapy, 3rd, Paris, France. (W. Warner, P.O. Box 819, Grand Central Station, New York 17)

*27–29.* Psychosomatic Aspects of Neoplastic Disease, 2nd annual conv., Paris, France. (L. L. LeShan, Intern. Psychosomatic Cancer Study Group, 144 E. 90 St., New York 28)

*27–31.* American Soc. of Plant Psysiologists, Lafayette, Ind. (C. O. Miller, Indiana Univ., Bloomington)

*27–1.* American Congr. of Physical

Medicine and Rehabilitation, Cleveland, Ohio. (D. C. Augustin, 30 N. Michigan Ave., Chicago 2, Ill.)

*27–1.* American Inst. of Biological Sciences, annual, Lafayette, Ind. (J. R. Olive, AIBS, 2000 P St., NW, Washington 6)

*27–1.* Coordination Chemistry, 6th intern. conf., Detroit, Mich. (S. Kirschner, Dept. of Chemistry, Wayne State Univ., Detroit 2)

*28–30.* Mathematical Assoc. of America, Stillwater, Okla. (H. L. Alder, MAA, Univ. of California, Davis)

*28–30.* Oak Ridge Inst. of Nuclear Studies, 8th annual summer symp., Gatlinburg, Tenn. (Symposium Office, University Relations Division, Oak Ridge Inst. of Nuclear Studies, P.O. Box 117, Oak Ridge, Tenn.)

*28–30.* Scandinavian Symp. on Fat Rancidity, 3rd, Sandefjord, Norway. (E. Törnudd, Gaustadallen 30, Blindern, Norway)

*28–31.* American Assoc. of Clinical Chemists, natl., New York, N.Y. (B. Klein, Chemistry Dept., Kingsbridge V.A. Hospital, Bronx, N.Y.)

*28–31,* American Soc. for Pharmacology and Experimental Therapeutics, Rochester, N.Y. (K. H. Beyer, Merck, Sharp and Dohme Research Laboratories, West Point, Pa.)

*28–31.* Botanical Soc. of America, Lafayette, Ind. (B. L. Turner, Dept. of Botany, Univ. of Texas, Austin 12)

*28–31.* Chemical Physics of Nonmetallic Crystals, intern. conf., Evanston, Ill. (O. C. Simpson, Argonne National Laboratory, 9700 South Cass Ave., Argonne, Ill.)

*28–1.* Heat Transfer Conf., intern., Boulder, Colo. (S. P. Kezios, American Soc. of Mechanical Engineers, 29 W. 39 St., New York 18)

*28–1.* Ionization Phenomena in Gases, 5th intern. conf., Munich, Germany. (Secretariat, Oskar von Miller Ring 18, P.O. 463, Munich 1)

*28–1.* Radioactive Metrology, symp., Oxford, England. (B. W. Robinson, Applied Physics Division, National Physical Laboratory, Teddington, Middlesex, England)

*28–1.* Rockets and Astronautics, 3rd intern. symp., Tokyo, Japan. (Japanese Rocket Soc., 1-3, Ginza-Nishi, Chuo-Ku, Tokyo)

*28–2.* European Soc. of Haematology, 8th congr., Vienna, Austria. (H. Fleischhracker, Frankgasse 8, Billrothhaus, Vienna 9)

*28–2.* International Assoc. of Medical Laboratory Technologists, general assembly, Stockholm, Sweden. (Miss M. Westenins, Statens Bakteriologiska Laboratorium, Box 764, Stockholm 1)

*28–2.* Detonation Waves, intern. colloquium, Gif-sur-Yvette, France. (G. M. Ribaud, Centre National de la Recherche Scientifique, 13 Quai Anatole France, Paris 7, France)

*28–2.* Mechanics of Turbulence, intern. colloquium, Marseilles, France. (A. Favre, Faculté des Sciences, Université, Marseilles)

*29.* American Soc. for Horticultural Science, Lafayette, Ind. (R. E. Marshall, Dept. of Horticulture, Michigan State Univ., East Lansing)

*(See issue of 16 June for comprehensive list)*

# New Products

*The information reported here is obtained from manufacturers and from other sources considered to be reliable. Neither* Science *nor the writer assumes responsibility for the accuracy of the information. All inquiries concerning items listed should be addressed to the manufacturer. Include the department number in your inquiry.*

■ TEMPERATURE-CONTROL SYSTEM is said to maintain temperature within ±0.2°C up to 1200°C. A platinum resistance thermometer, sealed to avoid contamination by gases, is used with an electronic controller to operate a saturable reactor that varies power input to the furnace windings. The electronic controller uses a slide-wire potentiometer that can be set with repeatability said to be one part in 4600. A 1-percent change in absolute temperature produces full-scale variation of control current. The same controller is used for furnaces of various capacities. Compensation for line voltage variation is provided. (Atkins Technical Inc., Dept. Sci212, 1276 W. 3rd St., Cleveland 13, Ohio)

■ MAGNETOMETER is said to be suitable for detecting magnetic anomalies of 0.1 gamma or less, and relays data in analog or digital form. In the digital mode, data are presented as a-c potentials varying in frequency with the polarity and magnitude of an ambient magnetic field. Sensitivity, in terms of deviation from a center operating frequency, is typically 2.5 parts in $10^5$ per gamma with an effective dynamic range of ±0.3 gauss. Analog data are presented as a-c signals varying in phase as the ambient magnetic field varies. Sensitivity is ±4 deg/gamma over a dynamic range of up to 20 gammas. Operating range may be increased with a corresponding reduction in sensitivity. The instrument is 7 in. long and 3 in. in diameter, and consumes 0.8 watt at 200 ma from a 4-volt d-c source. (Arnoux Corp., Dept. Sci208, 11924 W. Washington Blvd., Los Angeles 66, Calif.)

■ MICROSCOPES, featuring a completely integrated zoom optical system, provide a magnification range extending from 17.5 to 1940. The zoom optical system provides any magnification between 1 and 2 continuously. Six interchangeable bodies are available in the microscope series, including three monoculars, a binocular, a photo binocular, and a photomonocular. Focusing motion is applied to the stage so that the eye level remains constant. All bodies can be rotated through 360 deg on a common arm bracket. Eyepiece tubes are inclined. Cemented reflecting prisms are replaced by aluminum mirrors with protective coating. Attachments are available for 35-mm Polaroid Land cameras. These are focused through visual eyepiece tubes. A closed-type base accommodates interchangeably a variety of light sources. (Bausch and Lomb Inc., Dept. Sci215, Rochester 2, N.Y.)

■ HYDROGEN PURIFIERS produce pure hydrogen in milliliters per minute or cubic feet per hour quantities. In operation, an impure source gas containing free hydrogen flows under pressure into a stainless-steel jacket and over a bundle of palladium-silver alloy tubes. The tubes permit hydrogen to pass through their walls but bar all other gases. The alloy, unlike pure palladium, is said to exhibit no distortion when subjected to repeated heating and cooling cycles. Standard models for small volumes have capacities of 40 and 100 ml/min. The units operate on 115-volt a-c. (Milton Roy Co., Dept. Sci236, 1300 E. Mermaid Lane, Philadelphia 18, Pa.)

■ OXYGEN SENSOR operating on the polarographic principle measures partial pressure of oxygen from 0 to 760 mm-Hg with an absolute range of 250 to 1000 mm-Hg. Full-scale response time is said to be less than 10 sec at 70°F; operating temperature range is 40° to 150°F. The sensor is designed to be used with the manufacturer's airborne high-impedance amplifier. Custom-built units can be produced to order for use with microammeters or conventional recorders. (Beckman Instruments, Inc., Dept. Sci234, 2500 Harbor Blvd., Fullerton, Calit.)

■ TEMPERATURE CONTROLLER, designed for controlling the temperature of living specimens in medical and biological laboratories, uses a glass enclosed thermister of small mass to achieve rapid response. According to the manufacturer, any desired temperature between 25° to 50°C can be reproduced and indefinitely maintained within a few hundredths of a degree. Use to provide desired temperature environments for microscopic specimens during observation is suggested. (Oxford Laboratories, Dept. Sci238, 961 Woodside Rd., Redwood City, Calif.)

■ POWER SUPPLY provides an output range up to 350 kv and is designed for applications such as dielectric testing of cables and klystron apparatus. The unit is oil insulated. A continuous current of 8 ma is provided at any output voltage setting within the range of the equipment. Ripple is 2 percent (r.m.s.). Auxiliary filters are available to reduce ripple to 0.01 percent. (Sorensen & Co., Dept. Sci213, Richards Ave., South Norwalk, Conn.)

JOSHUA STERN

*National Bureau of Standards, Washington, D.C.*

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Box (give number)
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## POSITIONS WANTED

**Anatomist.** Ph.D. Desires position in medical college teaching neuroanatomy and microscopic anatomy. Member of professional societies and fraternities. Experienced in teaching and research. Box 139, SCIENCE. 6/30; 7/7, 14

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**Immunologist-Medical Microbiologist.** Teaching and research experience in academic institutions. Desires academic appointment with graduate faculty; research and teaching. Box 135, SCIENCE. 7/7, 14

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**Microbial Geneticist, Ph.D.** Phage transduction, transformation, animal viruses, tissue culture, molecular biology. Teaching and research. Box 147, SCIENCE. X

**Microbiologist, Ph.D.** 8 years' industrial experience, primarily in tissue culture and virology. Interested in academic or industrial appointment, Midwest or West. Box 143, SCIENCE. X

**Pharmacologist-Physiologist,** Senior, desires temporary appointment. Box 144, SCIENCE. X

**Plant Morphogenesis and Physiology.** Academic experience. Box 148, SCIENCE. X

## POSITIONS OPEN

**CHEMIST.** Preferably Ph.D., to teach general inorganic and organic chemistry at small but expanding liberal arts college. Start September 1961. For further information write to Academic Chairman

**University of Hawaii**
**Hilo Campus**
**Hilo, Hawaii**

### MEMORIAL UNIVERSITY OF NEWFOUNDLAND

**St. John's, Newfoundland, Canada**

Applications are invited for the position of Assistant Professor of Biology to give instruction primarily in Animal Physiology.

Candidates with background and experience in Marine Biology will receive preference. Ph.D. or equivalent essential. Duties beginning September 1961 to include teaching and research. The starting salary will be based on qualifications and experience.

Applications accompanied by complete curriculum vitae and the names of three referees should be addressed to the Head, Department of Biology, Memorial University of Newfoundland.

## POSITIONS OPEN

### CLINICAL MICROBIOLOGIST

Ph.D. preferred to supervise microbiology laboratory of large general hospital located in New York City. Opportunity for professional growth, research encouraged, university affiliation, salary about $9000 annually with liberal extras. Contact: Chief, Laboratory Service, Veterans Administration Hospital, 130 West Kingsbridge Road, Bronx 68, New York.

**MEDICAL and Scientific Publisher, Philadelphia, offers attractive college editorial position to college graduate. Knowledge of medical or biological sciences preferable. Territory includes Chicago and surrounding states, with occasional short nationwide trips. Liberal travel allowance. Residence optional—either Philadelphia or Chicago areas. Position entails obtaining new manuscripts and their evaluation for publication. Salary commensurate with experience. Write full particulars to Box 141, SCIENCE.**

### MICROBIOLOGIST

Ph.D. level. 260-bed general hospital. Salary $6000. Write to

**Dr. J. Ehrlich,** Director of Laboratory,
**Lebanon Hospital,**
**1650 Grand Concourse,**
**New York 57, New York.**

### PHYSIOLOGIST-PHARMACOLOGIST

Applications are invited for the position of senior research scientist in the Department of Pharmacology. The opening is for a Ph.D. with a strong background in physiology, who is creative and capable of independent investigation. The work involves initiating and conducting animal studies as part of a general program for evaluation of the effects of exogenous proteolytic enzymes, including studies on inflammation, wound healing, and immunological responses. We welcome applications from competent investigators even though they might lack specific training in the above list areas.

Reply in confidence giving full details, to **E. J. Reidy, Personnel Manager, Armour Pharmaceutical Company, Box 511, Kankakee, Illinois.**

### VIROLOGIST

To plan and conduct investigational, diagnostic, base-line, and surveillance studies of viruses and related organisms in the Hawaii state public health laboratory. Requires 2 years' experience in propagating, detecting, and identifying viruses and completion of graduate work leading to a Ph.D. in virology, bacteriology, or a related field. Salary $8256–$10,536 per annum. Write to Department of Personnel Services, 825 Mililani Street, Honolulu 13, Hawaii.

### PROFESSOR OF BIOCHEMISTRY

The University of Queensland invites applications for the position of professor of biochemistry. The applicant should hold a higher degree, preferably a doctorate, and have carried out research in the field of biochemistry, involving notable contribution to knowledge. He should have had experience of teaching biochemistry in a university.

The professor will be responsible for the organization and management of the university department of biochemistry which has recently moved to a new building at the main university site. Courses are offered to students in the faculties of medicine, dentistry, veterinary science, science and pharmacy, including an honors course for science students. The department is well equipped for both teaching and research and has adequate workshop facilities.

Salary will be at the rate of £A4000 per annum. The university has recently planned an electron microscope center and has ordered a Siemens and Halske model Elmiskop I for delivery in October 1961. A smaller "Akashi" electron microscope is available at present.

The successful applicant will be entitled to participate in the benefits available to the academic staff which include F.S.S.U. type superannuation, housing assistance, study leave, and travel grants.

Additional information on the conditions of appointment, staffing, and activities of the department, together with application forms, will be supplied upon request to C. J. Connell, Registrar, University of Queensland, St. Lucia, S.W.6, Queensland, Australia, with whom **applications close on 15 August.**

## THE COLONIAL SUGAR REFINING COMPANY LTD.

**Invites applications for the position of**
**INORGANIC RESEARCH CHEMIST**
**in the company's Research Department, Sydney, Australia**

**DUTIES:**

**The successful applicant will be required to investigate the chemistry and physical properties of minerals and inorganic substances. Experience in x-ray crystallography or in solid state reactions would be an advantage.**

**QUALIFICATIONS:**

**Candidates for the above position should have at least an Honors degree in chemistry, preferably with several years research experience.**

**SALARY:**

**Commencing salary within the range of £A1600 to £A2500 (3500 to 5500 dollars approx.) per annum, commensurate with qualifications and experience.**

**CONDITIONS:**

**The successful applicant will become eligible to join the company's Employees' Provident Fund after a probationary period and would be eligible to participate in the company's House Advance Scheme.**

**First-class fares to Sydney, Australia, will be provided for the successful applicant and family together with an amount of £A200 (450 dollars approx.) for transport of effects.**

**Applications in writing, quoting RD/13 and enclosing copies of references should be sent to:**

**The Chief Staff Officer,**
**Box 483, G.P.O.,**
**SYDNEY, N.S.W.**
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In addition to complete FLUORESTAR outfits, AO offers fluorescence accessories to equip your present AO Spencer bright field or phase microscope for dark field fluorescence.

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For complete information on the new FLUORESTAR and complete accessories for fluorescence microscopy write for our new Brochure SB12, or contact your AO Sales Representative. He is thoroughly trained in the techniques of fluorescence microscopy. Help with your specific problems is yours for the asking.

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